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=> file caplus
=> s Pim kinase and inhibitor
L1          9 PIM KINASE AND INHIBITOR

=> d ibib abs 1-9
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L1 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:542375 CAPLUS Full-text
TITLE: Pim kinase substrate identification and specificity
AUTHOR(S): Peng, Charline; Knebel, Axel; Morrice, Nick A.; Li, Xiang; Barringer, Kevin; Li, Jun; Jakes, Scott; Werneburg, Brian; Wang, Lian
CORPORATE SOURCE: Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, 06877, USA
SOURCE: Journal of Biochemistry (Tokyo, Japan) (2007), 141(3), 353-362
CODEN: JOBIAO; ISSN: 0021-924X
PUBLISHER: Japanese Biochemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The Pim family of Ser/Thr kinases has been implicated in the process of lymphomagenesis and cell survival. Known substrates of Pim kinases are few and poorly characterized. In this study we set out to identify novel Pim-2 substrates using the Kinase Substrate Tracking and Elucidation (KESTREL) approach. Two potential substrates, eukaryotic initiation factor 4B (eIF4B) and apoptosis inhibitor 5 (API-5), were identified from rat thymus exts. Sequence comparison of the Pim-2 kinase phosphorylation sites of eIF4B and mouse BAD, the only other known Pim-2 substrate, revealed conserved amino acids preceding the phosphorylated serine residue. Stepwise replacement of the conserved residues produced a consensus sequence for Pim kinase recognition: RXRHXS. Pim-1 and Pim-2 catalyzed the phosphorylation of this recognition sequence 20-fold more efficiently than the original (K/R-K/R-R-K/R-L-S/T-a; a = small chain amino acid) Pim-1 phosphorylation site. The identification of the novel Pim kinase consensus sequence provides a more sensitive and versatile peptide based assay for screening modulators of Pim kinase activity.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:409638 CAPLUS Full-text
DOCUMENT NUMBER: 146:422003
TITLE: Pyrazolo[1,5-a]pyrimidine compounds as protein kinase inhibitors and their preparation, pharmaceutical compositions and their use in the treatment of protein kinase-mediated diseases
INVENTOR(S): Guzi, Timothy J.; Paruch, Kamil; Dwyer, Michael P.; Parry, David A.
PATENT ASSIGNEE(S): Schering Corp., USA
SOURCE: U.S. Pat. Appl. Publ., 340pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2007082900	A1	20070412	US 2006-542801	20061004
WO 2007044441	A2	20070419	WO 2006-US38917	20061004

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2005-724158P P 20051006
OTHER SOURCE(S): MARPAT 146:422003

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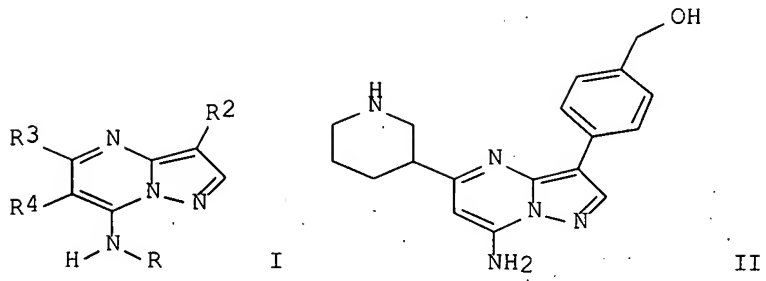

AB The invention provides methods for inhibiting protein kinases selected from the group consisting of AKT, CHeckpoint kinase, Aurora kinase, Pim kinases, and tyrosine kinase using pyrazolo[1,5-a]pyrimidine compds. of formula I, and methods of treatment, prevention, inhibition, or amelioration of one or more diseases associated with protein kinases using such compds. Compds. of formula I wherein R is H, alkyl, alkenyl, alkynyl, aralkyl, arylalkenyl, cycloalkyl, cycloalkylalkyl, alkenylalkyl, etc.; R2 is H, alkyl, alkenyl, alkynyl, CF3, heterocyclyl(alkyl), halo, haloalkyl, (hetero)aryl(alkyl), etc.; R3 is H, halo, NH2 and derivs., OH and derivs., SH and derivs., CONH2 and derivs., alkyl, alkynyl, cycloalkyl, (hetero)aryl, etc.; R4 is H and alkyl; and their pharmaceutically acceptable salts, solvates, esters and prodrugs thereof, are claimed. Example compound II was prepared by a multistep procedure (procedure given). All the invention compds. were evaluated for their protein kinase inhibitory activity.

L1 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:371907 CAPLUS Full-text
DOCUMENT NUMBER: 145:246726
TITLE: Regulation of cytokine signaling
AUTHOR(S): Vuong, Bao Q.; McKeag, Lisa; Losman, Julie A.; Li, Jianze; Banks, Alex; Fay, Scott; Chen, Peter; Rothman, Paul
CORPORATE SOURCE: Departments of Medicine and Microbiology, College of Physicians and Surgeons, Columbia University, New York, NY, USA
SOURCE: Cell Signaling in Vascular Inflammation (2005), 103-111. Editor(s): Bhattacharya, Jahar. Humana Press Inc.: Totowa, N. J.
CODEN: 69IAML; ISBN: 1-58829-525-7
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review. Cytokines are important modulators of the immune response that underlies the inflammatory process in atopic forms of asthma. Interleukin (IL)-4 and IL-13 are important cytokines for the regulation of these asthmatic immune responses. However, the cellular mechanisms that regulate IL-4 and IL-13 signaling remain unknown. Recently, a new family of proteins, termed suppressors of cytokine signaling (SOCS), has been identified. We have previously shown that SOCS-1 is a potent inhibitor of JAK-STAT signaling activated by IL-4. SOCS-1 expression is regulated both at the RNA and protein stability level. To identify proteins that bind and potentially regulate SOCS-1, we used the yeast two-hybrid system. We have identified the serine-threonine kinase Pim-2 as a binding partner for SOCS-1. Our preliminary studies demonstrate that SOCS-1 can interact with all three Pim kinases in mammalian cells. Co-expression of SOCS-1 with Pim kinases leads to the expression of novel SOCS-1 isoforms to require serine-threonine kinase activity. Pim kinases can directly phosphorylate SOCS-1. In addition, co-expression of SOCS-1 with Pim-2 increases the levels of SOCS-1 protein. Finally, expression of Pim-2 increases the inhibition of IL-4 signaling by SOCS-1. These data lead to a model by which the expression of Pim kinases alters SOCS-1 function through a phosphorylation event that stabilizes the SOCS-1 protein. This chapter proposes expts. to test this model and determine the role Pim kinases play in regulating IL-4 signaling in vivo. In addition, we propose to study the role of Pim kinases in a murine model of asthma.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:307888 CAPLUS Full-text
DOCUMENT NUMBER: 144:465425
TITLE: Targeting PIM Kinases Impairs Survival of Hematopoietic Cells Transformed by Kinase

Inhibitor-Sensitive and Kinase Inhibitor-Resistant Forms of Fms-Like Tyrosine Kinase 3 and BCR/ABL

AUTHOR(S): Adam, Myriam; Pogacic, Vanda; Bendit, Marina; Chappuis, Richard; Nawijn, Martijn C.; Duyster, Justus; Fox, Casey J.; Thompson, Craig B.; Cools, Jan; Schwaller, Juerg

CORPORATE SOURCE: Department of Pathology, Geneva Medical School, Geneva, Switz.

SOURCE: Cancer Research (2006), 66(7), 3828-3835
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Previous studies have shown that activation of the signal transducer and activator of transcription 5 (STAT5) plays an essential role in leukemogenesis mediated through constitutive activated protein tyrosine kinases (PTK). Because PIM-1 is a STAT5 target gene, we analyzed the role of the family of PIM serine/threonine kinases (PIM-1 to PIM-3) in PTK-mediated transformation of hematopoietic cells. Ba/F3 cells transformed to growth factor independence by various oncogenic PTKs (TEL/JAK2, TEL/TRKC, TEL/ABL, BCR/ABL, FLT3-ITD, and H4/PDGFβR) show abundant expression of PIM-1 and PIM-2. Suppression of PIM-1 activity had a negligible effect on transformation. In contrast, expression of kinase-dead PIM-2 mutant (PIM-2KD) led to a rapid decline of survival in Ba/F3 cells transformed by FLT3-ITD but not by other oncogenic PTKs tested. Coexpression of PIM-1KD and PIM-2KD abrogated growth factor-independent growth of Ba/F3 transformed by several PTKs, including BCR/ABL. Targeted down-regulation of PIM-2 by RNA interference (RNAi) selectively abrogated survival of Ba/F3 cells transformed by various Fms-like tyrosine kinase 3 (FLT3)-activating mutants [internal tandem duplication (ITD) and kinase domain] and attenuated growth of human cell lines containing FLT3 mutations. Interestingly, cells transformed by FLT3 and BCR/ABL mutations that confer resistance to small-mol. tyrosine kinase inhibitors were still sensitive to knockdown of PIM-2, or PIM-1 and PIM-2 by RNAi. Our observations indicate that combined inactivation of PIM-1 and PIM-2 interferes with oncogenic PTKs and suggest that PIMs are alternative therapeutic targets in PTK-mediated leukemia. Targeting the PIM kinase family could provide a new avenue to overcome resistance against small-mol. tyrosine kinase inhibitors .

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:1302374 CAPLUS Full-text

DOCUMENT NUMBER: 144:186982

TITLE: Structure and Substrate Specificity of the Pim-1 Kinase

AUTHOR(S): Bullock, Alex N.; Debreczeni, Judit; Amos, Ann L.; Knapp, Stefan; Turk, Benjamin E.

CORPORATE SOURCE: Centre for Structural Genomics, Botnar Research Centre, Oxford University, Oxford, OX3 7LD, UK

SOURCE: Journal of Biological Chemistry (2005), 280(50), 41675-41682
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The Pim kinases are a family of three vertebrate protein serine/threonine kinases (Pim-1, -2, and -3) belonging to the CAMK (calmodulin-dependent protein kinase-related) group. Pim kinases are emerging as important mediators of cytokine signaling pathways in hematopoietic cells, and they contribute to the progression of certain leukemias and solid tumors. A number of cytoplasmic and nuclear proteins are phosphorylated by Pim kinases and may act as their effectors in normal physiol. and in disease. Recent crystallog. studies of Pim-1 have identified unique structural features but have not provided insight into how the kinase recognizes its target substrates. Here, we have conducted peptide library screens to exhaustively determine the sequence specificity of active site-mediated phosphorylation by Pim-1 and Pim-3. We have identified the major site of Pim-1 autophosphorylation and find surprisingly that it maps to a novel site that diverges from its consensus phosphorylation motif. We have solved the crystal structure of Pim-1 bound to a high affinity peptide substrate in complexes with either the ATP analog AMP-PNP or the bisindolylmaleimide kinase inhibitor 2-[1-(3-dimethylaminopropyl)-1H-indol-3-yl]-3-(1H-indol-3-yl)maleimide HCl. These structures reveal an unanticipated mode of recognition for basic residues upstream of the phosphorylation site, distinct from that of other kinases with similar substrate specificity. The structures provide a rationale for the unusually high affinity of Pim kinases for peptide substrates and suggest a general mode for substrate binding to members of the CAMK group.

REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:822066 CAPLUS Full-text
DOCUMENT NUMBER: 143:206429
TITLE: Screening for effectors of PIM kinases for treatment of urinary incontinence
INVENTOR(S): Christoph, Thomas
PATENT ASSIGNEE(S): Gruenenthal GmbH, Germany
SOURCE: Ger. Offen., 37 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 102004004894	A1	20050818	DE 2004-102004004894	20040130
PRIORITY APPLN. INFO.:			DE 2004-102004004894	20040130

AB Methods for identifying effectors of the PIM-1 or PIM-3 kinases that can be used to treat urinary incontinence or the urge to frequent urination are described. These effectors may include inhibitors of kinase gene expression, or therapeutic alleles of the gene, antibodies to the protein, small mol. drugs, or aptamers. Alleles of the kinase gene may also be used as diagnostic markers for these diseases. Knockout of the PIM-1 gene in mice leads to changes in urination behavior with PIM-1 deficient mice showing a distinct lowering of frequency of urination. Methods of using strips of bladder to study the effects of PIM kinase inhibitors on contraction of cell wall muscle are described.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:469086 CAPLUS Full-text
TITLE: A pim kinase inhibitor, please
AUTHOR(S): Giles, Francis
CORPORATE SOURCE: Anderson Cancer Center
SOURCE: Blood (2005), 105(11), 4158-4159
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hammerman and colleagues have shown that the Pim-2 kinase is required to confer rapamycin resistance in hematopoietic cells, thus providing a strong rationale for the development of Pim kinase inhibitors as potential therapeutic agents in hematol. malignancies.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:106619 CAPLUS Full-text
DOCUMENT NUMBER: 138:350472
TITLE: Protein Phosphatase 2A Regulates the Stability of Pim Protein Kinases
AUTHOR(S): Losman, Julie A.; Chen, X. Peter; Vuong, Bao Q.; Fay, Scott; Rothman, Paul B.
CORPORATE SOURCE: Integrated Program in Molecular, Cellular, and Biophysical Studies, Columbia University, College of Physicians and Surgeons, New York, NY, 10032, USA
SOURCE: Journal of Biological Chemistry (2003), 278(7), 4800-4805
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The pim family of proto-oncogenes encodes three serine-threonine kinases that have been implicated in the development of malignancies in mice and in humans. Expression of the Pim protein kinases is tightly regulated at the transcriptional, post-transcriptional, and translational levels. Dysregulation of pim transcription and pim mRNA stability have been implicated in Pim-mediated transformation. Data presented herein demonstrate that expression of the Pim kinases is addnl. regulated at the post-translational level, by the serine-threonine phosphatase protein phosphatase 2A (PP2A). The catalytic subunit of PP2A assocs. with the Pim kinases in vivo, and the Pim kinases are substrates of PP2A phosphatase activity in vitro. Furthermore, overexpression of PP2A reduces the levels of the Pim proteins, whereas inhibition of PP2A activity by the protein phosphatase inhibitor okadaic acid stabilizes the Pim proteins. Finally, the effects of PP2A on the expression of the Pim proteins can affect Pim function. Taken together, these data suggest that PP2A activity is important for the regulation of the stability and function of the Pim kinases.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:539652 CAPLUS Full-text
DOCUMENT NUMBER: 137:88453
TITLE: Pim kinase-related methods for treatment of an allergic response, asthma, and transplant rejection
INVENTOR(S): Rothman, Paul; Chen, Peter
PATENT ASSIGNEE(S): The Trustees of Columbia University In the City of New York, USA
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002055489	A2	20020718	WO 2001-US50535	20011227
WO 2002055489	A3	20021003		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002246864	A1	20020724	AU 2002-246864	20011227
US 2004109868	A1	20040610	US 2004-250380	20040120
PRIORITY APPLN. INFO.:			US 2000-258421P P	20001227
			WO 2001-US50535 W	20011227

AB The invention provides methods for treating an allergic response, asthma, and the onset of transplant rejection in a subject. The methods involve administering an agent which increases the amount and/or the activity of a Pim kinase. The invention also provides a method for determining whether an agent increases the phosphorylation of a Socs-1 protein by a Pim kinase.

=> s kinase and inhibitor
L2 98409 KINASE AND INHIBITOR

=> s l2 and atp
L3 6731 L2 AND ATP

=> s l3 and structure activity
L4 337 L3 AND STRUCTURE ACTIVITY

=> s l4 not 2002-2007/py
L5 122 L4 NOT 2002-2007/PY

=> s l4 and relationship
L6 326 L4 AND RELATIONSHIP

=> s l6 not 2002-2007/py
L7 114 L6 NOT 2002-2007/PY

=> d ibib abs 1-114

L7 ANSWER 1 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:132148 CAPLUS Full-text
DOCUMENT NUMBER: 136:318825
TITLE: Pyrrolo[2,3-d]pyrimidine and pyrazolo[3,4-d]pyrimidine derivatives as selective inhibitors of the EGF receptor tyrosine kinase
AUTHOR(S): Caravatti, G.; Bruggen, J.; Buchdunger, E.; Cozens, R.; Furet, P.; Lydon, N.; O'Reilly, T.; Traxler, P.
CORPORATE SOURCE: TA Oncology, Novartis Pharma AG, Basel, CH-4002, Switz.
SOURCE: ACS Symposium Series (2001), 796(Anticancer Agents),

231-244
CODEN: ACSMC8; ISSN: 0097-6156
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:318825
AB The EFG receptor tyrosine kinase (EGFR) is an attractive target for the development of agents directed against tumors which either overexpress the EGFR or which have a mutated or amplified gene encoding the EGFR. Several ATP-competitive inhibitors of this kinase have shown promising in vitro and in vivo efficacy and are currently in different stages of clin. development. One of them is PKI166, a pyrrolo[2,3-d]pyrimidine, which has been selected from a large series of pyrrolo[2,3-d]pyrimidines and structurally related pyrazolo[3,4-d]pyrimidines. The discovery and preclin. data of PKI166 are summarized.
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:67145 CAPLUS Full-text
DOCUMENT NUMBER: 136:305890
TITLE: Flavones inhibit the hexameric replicative helicase RepA
AUTHOR(S): Xu, Hai; Ziegelin, Gunter; Schroder, Werner; Frank, Joachim; Ayora, Sylvia; Alonso, Juan Carlos; Lanka, Erich; Saenger, Wolfram
CORPORATE SOURCE: Institut fuer Kristallographie, Freie Universitat Berlin, Berlin, D-14195, Germany
SOURCE: Nucleic Acids Research (2001), 29(24), 5058-5066
CODEN: NARHAD; ISSN: 0305-1048
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Helicases couple the hydrolysis of nucleoside triphosphates (NTPs) to the unwinding of double-stranded nucleic acids and are essential in DNA metabolism Thus far, no inhibitors are known for helicases except heliquinomycin isolated from Streptomyces sp. As the three-dimensional structure of the hexameric replicative DNA helicase RepA encoded by the broad host-range plasmid RSF1010 is known, this protein served as a model helicase to search for inhibitory compds. The com. available flavone derivs. luteolin, morin, myricetin and dimyricetin (an oxidation product of myricetin) inhibited the ATPase and double-stranded DNA unwinding activities of RepA. Dimyricetin was the most effective inhibitor for both activities. Single-stranded DNA-dependent RepA ATPase activity is inhibited noncompetitively by all four compds. This finding contrasts the inhibition of phosphoinositide 3-kinase by flavones that fit into the ATP binding pocket of this enzyme. Myricetin also inhibited the growth of a Gram-pos. and a Gram-neg. bacterial species. As the authors found other hexameric and nonhexameric prokaryotic helicases to be differentially sensitive to myricetin, flavones may provide substructures for the design of mols. helpful for unraveling the mechanism of helicase action and of novel pharmacol. useful mols.
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:45330 CAPLUS Full-text
DOCUMENT NUMBER: 136:318821
TITLE: 1,4-dioxane-fused 4-anilinoquinazoline as inhibitors of epidermal growth factor receptor kinase
AUTHOR(S): Lee, Jae Yeol; Park, Yong Kyu; Seo, Seon Hee; So, In-Seop; Chung, Hee-Kyung; Yang, Beom-Seok; Lee, Sook Ja; Park, Hokoon; Lee, Yong Sup
CORPORATE SOURCE: Medicinal Chemistry Research Center, Korea Institute of Science and Technology, Seoul, 130-650, S. Korea
SOURCE: Archiv der Pharmazie (Weinheim, Germany) (2001), 334(11), 357-360
CODEN: ARPMAS; ISSN: 0365-6233
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
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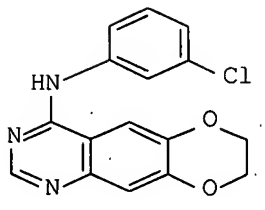

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AB The 4-anilinoquinazoline PD 153035 is a potential antitumor agent which acts by inhibiting tyrosine kinase activity of epidermal growth factor receptor (EFGR) via competitive binding at the ATP site of enzyme. A series of cyclic analogs of PD 153035 bearing the 1,4-dioxane ring was prepared These were evaluated for their ability to inhibit the EGFR kinase and the growth of primary human tumor cell cultures. All of the new 4-anilinoquinazolines exhibited less potency than PD 153035 against EGFR kinase. However, several compds. showed higher inhibitory activities than PD 153035 against the growth of A431 tumor cell line. I was as potent as PD 153035 against EGFR kinase and showed about 5.4-fold better potency than PD153035 in the inhibition of growth of A431 cell line with good selectivity.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:2114 CAPLUS Full-text
DOCUMENT NUMBER: 136:179728
TITLE: Inhibition of epidermal growth factor receptor tyrosine kinase by chalcone derivatives
AUTHOR(S): Yang, Er Bin; Guo, Yong Jian; Zhang, Kai; Chen, Yu Zong; Mack, Peter
CORPORATE SOURCE: Department of Experimental Surgery, Singapore General Hospital, Singapore, 169608, Singapore
SOURCE: Biochimica et Biophysica Acta, Protein Structure and Molecular Enzymology (2001), 1550(2), 144-152
CODEN: BBAEDZ; ISSN: 0167-4838
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In our previous study, butein, a chalcone derivative, was found to be an inhibitor of tyrosine kinases and the inhibition was ATP-competitive. In this work, chalcone and seven chalcone derivs. were used to analyze the relationship between the structure of these compds. and their inhibition of tyrosine kinase activity. Three of chalcone derivs., including butein, marein and phloretin, were found to have an ability to inhibit the tyrosine kinase activity of epidermal growth factor receptor (EGFR) in vitro. IC50 was 8 μM for butein, 19 μM for marein and 25 μM for phloretin. The structural characterizations of these inhibitors suggest that the hydroxylations at C4 and C4' of these mols. may be required for them to act as EGFR tyrosine kinase inhibitors. The inhibition of EGF-induced EGFR tyrosine phosphorylation by butein was also observed in human hepatocellular carcinoma HepG2 cells, while marein and phloretin were inactive at the doses tested. Mol. modeling suggests that butein, marein and phloretin can be docked into the ATP binding pocket of EGFR. Hydrogen bonds and hydrophobic interaction appear to be important in the binding of these inhibitors to EGFR.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:892349 CAPLUS Full-text
DOCUMENT NUMBER: 136:146987
TITLE: A Novel Approach for the Development of Selective Cdk4 Inhibitors: Library Design Based on Locations of Cdk4 Specific Amino Acid Residues
AUTHOR(S): Honma, Teruki; Yoshizumi, Takashi; Hashimoto, Noriaki; Hayashi, Kyoko; Kawanishi, Nobuhiko; Fukasawa, Kazuhiro; Takaki, Tohru; Ikeura, Chinatsu; Ikuta, Mari; Suzuki-Takahashi, Ikuko; Hayama, Takashi; Nishimura, Susumu; Morishima, Hajime
CORPORATE SOURCE: Banyu Tsukuba Research Institute in collaboration with Merck Research Laboratories, Tsukuba, Ibaraki, 300-2611, Japan
SOURCE: Journal of Medicinal Chemistry (2001), 44(26),

4628-4640
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:146987
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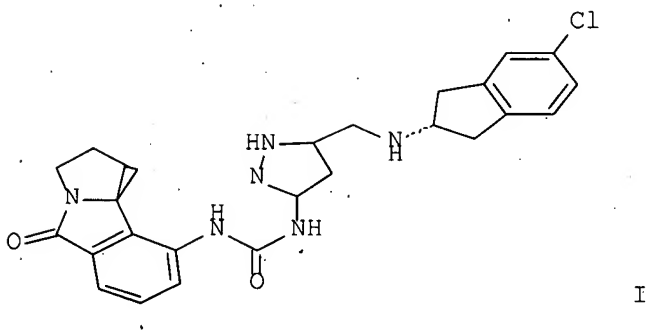

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AB Identification of a selective inhibitor for a particular protein kinase without inhibition of other kinases is critical for use as a biol. tool or drug. However, this is very difficult because there are hundreds of homologous kinases and their kinase domains including the ATP binding pocket have a common folding pattern. To address this issue, the authors applied the following structure-based approach for designing selective Cdk4 inhibitors : (1) identification of specifically altered amino acid residues around the ATP binding pocket in Cdk4 by comparison of 390 representative kinases, (2) prediction of appropriate positions to introduce substituents in lead compds. based on the locations of the altered amino acid residues and the binding modes of lead compds., and (3) library design to interact with the altered amino acid residues supported by de novo design programs. Accordingly, Asp99, Thr102, and Gln98 of Cdk4, which are located in the p16 binding region, were selected as first target residues for specific interactions with Cdk4. Subsequently, the 5-position of the pyrazole ring in the pyrazol-3-ylurea class of lead compound was predicted to be a suitable position to introduce substituents. The authors then designed a chemical library of pyrazol-3-ylurea substituted with alkylaminomethyl groups based on the output structures of de novo design programs. Thus the authors identified a highly selective and potent Cdk4 inhibitor (I), substituted with a 5-chloroindan-2-ylaminomethyl group. Compound I showed higher selectivity on Cdk4 over those on not only Cdk1/2 (780-fold/190-fold) but also many other kinases (>430-fold) that have been tested thus far. The structural basis for Cdk4 selective inhibition by I was analyzed by combining mol. modeling and the x-ray anal. of the Cdk4 mimic Cdk2- inhibitor complex. The results suggest that the hydrogen bond with the carboxyl group of Asp99 and hydrophobic van der Waals contact with the side chains of Thr102 and Gln98 are important. Compound I was found to cause cell cycle arrest of the Rb(+) cancer cell line in the G1 phase, indicating that it is a good biol. tool.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 6 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:892345 CAPLUS Full-text
DOCUMENT NUMBER: 136:128595
TITLE: Structure-Based Generation of a New Class of Potent Cdk4 Inhibitors: New de Novo Design Strategy and Library Design
AUTHOR(S): Honma, Teruki; Hayashi, Kyoko; Aoyama, Tetsuya; Hashimoto, Noriaki; Machida, Takumitsu; Fukasawa, Kazuhiro; Iwama, Toshiharu; Ikeura, Chinatsu; Ikuta, Mari; Suzuki-Takahashi, Ikuko; Iwasawa, Yoshikazu; Hayama, Takashi; Nishimura, Susumu; Morishima, Hajime
CORPORATE SOURCE: Banyu Tsukuba Research Institute in collaboration with Merck Research Laboratories, Ibaraki, 300-2611, Japan
SOURCE: Journal of Medicinal Chemistry (2001), 44(26), 4615-4627
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

OTHER SOURCE(S): CASREACT 136:128595

AB As a first step in structure-based design of highly selective and potent Cdk4 inhibitors, we performed structure-based generation of a novel series of Cdk4 inhibitors. A Cdk4 homol. model was constructed according to x-ray anal. of an activated form of Cdk2. Using this model, we applied a new de novo design strategy which combined the de novo design program LEGEND with our inhouse structure selection supporting system SEEDS to generate new scaffold candidates. In this way, four classes of scaffold candidates including diarylurea were identified. By constructing diarylurea informer libraries based on the structural requirements of Cdk inhibitors in the ATP binding pocket of the Cdk4 model, we were able to identify a potent Cdk4 inhibitor N-(9-oxo-9H-fluoren-4-yl)-N'-pyridin-2-ylurea (I) with IC50 = 0.10 μM, together with preliminary SAR. We performed a docking study between I and the Cdk4 model and selected a reasonable binding mode which is consistent with the SAR. Further modification based on the proposed binding mode provided a more potent compound, N-[(9bR)-5-oxo- 2,3,5,9b-tetrahydro-1H-pyrrolo[2,1-a]isoindol-9-yl]-N'-pyridin-2-ylurea (II) with IC50 = 0.042 μM, x-ray anal. of which was accomplished by the soaking method. The predicted binding mode of I in Cdk4 was validated by x-ray anal. of the Cdk2-II complex.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:775552 CAPLUS Full-text

DOCUMENT NUMBER: 136:48577

TITLE: The TGFβ receptor activation process: an inhibitor- to substrate-binding switch

AUTHOR(S): Huse, Morgan; Muir, Tom W.; Xu, Lan; Chen, Ye-Guang; Kuriyan, John; Massague, Joan

CORPORATE SOURCE: Laboratory of Molecular Biophysics, Rockefeller University, New York, NY, 10021, USA

SOURCE: Molecular Cell (2001), 8(3), 671-682
CODEN: MOCEFL; ISSN: 1097-2765

PUBLISHER: Cell Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The type I TGFβ receptor (TβR-I) is activated by phosphorylation of the GS region, a conserved juxtamembrane segment located just N-terminal to the kinase domain. The authors have studied the mol. mechanism of receptor activation using a homogeneously tetra-phosphorylated form of TβR-I, prepared using protein semi-synthesis. Phosphorylation of the GS region dramatically enhances the specificity of TβR-I for the critical C-terminal serines of Smad2. In addition, tetra-phosphorylated TβR-I is bound specifically by Smad2 in a phosphorylation-dependent manner and is no longer recognized by the inhibitory protein FKBP12. Thus, phosphorylation activates TβR-I by switching the GS region from a binding site for an inhibitor into a binding surface for substrate. The authors' observations suggest that phosphoserine/phosphothreonine-dependent localization is a key feature of the TβR-I/Smad activation process.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:639899 CAPLUS Full-text

TITLE: Design, synthesis, and structure-activity relationship studies of novel cyclin dependent kinases (CDKs) inhibitors

AUTHOR(S): Tedder, Martina E.; Dumas, David P.; Bang, Chan S.; Coulter, Daniel; Yang, Jae Y.; Chen, Xiaohua; Cao, Xiaodong

CORPORATE SOURCE: Medicinal Chemistry, LG Biomedical Institute, La Jolla, CA, 92037, USA

SOURCE: Abstracts of Papers, 222nd ACS National Meeting, Chicago, IL, United States, August 26-30, 2001 (2001), MEDI-080. American Chemical Society: Washington, D. C.
CODEN: 69BUZP

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB Cyclin dependent kinases (CDKs) are a class of cell cycle proteins which activate host proteins through phosphorylation on serine or threonine using ATP (ATP) as a phosphate donor. Since they control cell cycle progression in proliferating cells, the inhibition of CDKs can represent a therapeutic approach to the intervention of proliferative disorders such as cancer. A novel series of CDKs inhibitors has been synthesized and tested. Some of these compds. inhibited CDKs with an IC50 value in the low nanomolar range. The synthesis, structure activity relationship and selectivity among different types of CDKs of these novel compds. will be presented.

L7 ANSWER 9 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:621553 CAPLUS Full-text
DOCUMENT NUMBER: 135:352200
TITLE: Rational design of potent and selective EGFR tyrosine kinase inhibitors as anticancer agents
AUTHOR(S): Ghosh, Sutapa; Liu, Xing-Ping; Zheng, Yaguo; Uckun, Fatih M.
CORPORATE SOURCE: Parker Hughes Cancer Center, St. Paul, MN, 55113, USA
SOURCE: Current Cancer Drug Targets (2001), 1(2), 129-140
CODEN: CCDTB9; ISSN: 1568-0096
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with refs. is given. Increasing knowledge of the structure and function of the epidermal growth factor receptor (EGFR) subfamily of tyrosine kinases, and of their role in the initiation and progression of various cancers has led to the search for inhibitors of signaling mols. that may prove to be important in cancer therapy. The complex nature of EGFR biol. allows for potential opportunities for EGFR inhibitors in a number of areas of cancer therapy, including proliferative, angiogenic, invasive, and metastatic aspects. Different approaches were used to target either the extracellular ligand-binding domain of the EGFR or the intracellular tyrosine kinase region that results in interference with its signaling pathways that modulate cancer-promoting responses. Examples of these include a number of monoclonal antibodies, immunotoxins, and ligand-binding cytotoxic agents that target the extracellular ligand binding region of EGFR, and small mol. inhibitors that target the intracellular kinase domain and act by interfering with ATP binding to the receptor. During the past 3 yr, significant progress was made towards the identification of new structural classes of small mol. inhibitors that show high potency and specificity towards EGFR. The search for new small mols. that inhibit kinases has included traditional approaches like the testing of natural products, random screening of chemical libraries, the use of classical structure-activity-relationship studies, and the incorporation of structure-based drug design and combinatorial chemical techniques. There was a significant improvement in the development of selective EGFR inhibitors with the use of a structure-based design approach employing a homol. model of the EGFR kinase domain. Mol. modeling procedures were used to generate novel mols. that are complementary in shape and electrostatics to the EGFR kinase domain topog. This review focuses on some examples of the successful use of this method.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 10 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:516932 CAPLUS Full-text
DOCUMENT NUMBER: 135:313144
TITLE: The 4-anilinoquinazoline class of inhibitors of the erbB family of receptor tyrosine kinases
AUTHOR(S): Denny, William A.
CORPORATE SOURCE: Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, N. Z.
SOURCE: Farmaco (2001), 56(1-2), 51-56
CODEN: FRMCE8; ISSN: 0014-827X
PUBLISHER: Elsevier Science S.A.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The erbB family of receptor tyrosine kinase enzymes, and particularly EGFR and HER2/neu, have become important targets for potential anticancer drugs. The substrate protein binding site theor. is the more attractive intracellular target on these enzymes, possessing lower homol. than the ATP site between different receptor kinases. However, a major breakthrough in this field was the discovery that 4-anilinoquinazolines are potent and selective inhibitors, despite binding at the ATP site. The very tight structure-activity relationships shown by these compds. suggested a clearly-defined binding mode, where the quinazoline ring binds in the adenine pocket and the anilino ring binds in an adjacent, unique lipophilic pocket. A unique cysteine (Cys-773) adjacent to the quinazoline binding site has prompted the development of irreversible inhibitors that target this residue. Three 4-anilinoquinazoline analogs (two reversible and one irreversible inhibitor) have been evaluated clin. as anticancer drugs. Data from the most advanced, the reversible inhibitor Iressa, suggest that this class of compds. may be of value in cancer chemotherapy.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 11 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:454011 CAPLUS Full-text
DOCUMENT NUMBER: 135:177179
TITLE: Thymidylate kinase of Mycobacterium tuberculosis: a chimera sharing properties common to eukaryotic and bacterial enzymes
AUTHOR(S): Munier-Lehmann, Helene; Chaffotte, Alain; Pochet,

Sylvie; Labesse, Gilles
CORPORATE SOURCE: Laboratoire de Chimie Structurale des Macromolecules, Institut Pasteur, Paris, 75724, Fr.
SOURCE: Protein Science (2001), 10(6), 1195-1205
CODEN: PRCIEI; ISSN: 0961-8368
PUBLISHER: Cold Spring Harbor Laboratory Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have overexpressed in Escherichia coli the thymidylate kinase of Mycobacterium tuberculosis (TMPKmt). Biochem. and physico-chemical characterization of TMPKmt revealed distinct structural and catalytic features when compared to its counterpart from yeast (TMPKy) or E. coli (TMPKec). Denaturation of the dimeric TMPKmt by urea under equilibrium conditions was studied by intrinsic fluorescence and CD spectroscopy. It suggested a three-state unfolding mechanism with a monomeric intermediate. On the other hand, 3'-azido-3'-deoxythymidine monophosphate (AZT-MP), which is substrate for TMPKy and TMPKec acts as a potent competitive inhibitor for TMPKmt. We propose a structural model of TMPKmt in which the overall fold described in TMPKy and TMPKec is conserved and slight differences at the level of primary and 3D-structure explain strong variations in the phosphorylation rate of substrate analogs. According to the model, we synthesized dTMP analogs acting either as substrates or specific inhibitors of TMPKmt. This approach based on slight structural differences among similar proteins could be applied to other essential enzymes for the design of new species-specific antimicrobials.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 12 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:400644 CAPLUS Full-text
DOCUMENT NUMBER: 135:189735
TITLE: Identification of cyclin-dependent kinase 1 inhibitors of a new chemical type by structure-based design and database searching
AUTHOR(S): Furet, Pascal; Meyer, Thomas; Mittl, Peer; Fretz, Heinz
CORPORATE SOURCE: Oncology Research Department, Novartis Pharma Inc., Basel, CH-4002, Switz.
SOURCE: Journal of Computer-Aided Molecular Design (2001), 15(5), 489-495
CODEN: JCADEQ; ISSN: 0920-654X
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have selected cyclin-dependent kinase 1 (CDK1), an enzyme participating in the regulation of the cell cycle, as a target in our efforts to discover new antitumor agents. By exploiting available structural information, we designed an ATP-site directed ligand scaffold that allowed us to identify 4-(3-methyl-1,4-dioxo-1,4-dihydro- naphthalen-2-ylamino)benzenesulfonamide as a new potent inhibitor of CDK1 in a subsequent database search. The synthesis and testing of some analogs confirmed the interest of this class of compds. as novel CDK1 inhibitors.
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 13 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:372383 CAPLUS Full-text
DOCUMENT NUMBER: 135:118641
TITLE: Structural Determinants for Potent, Selective Dual Site Inhibition of Human pp60c-src by 4-Anilinoquinazolines
AUTHOR(S): Tian, Gaochao; Cory, Michael; Smith, Albert A.; Knight, W. Blaine
CORPORATE SOURCE: Departments of Molecular Biochemistry and Structural Chemistry, GlaxoSmithKline Research and Development, Research Triangle Park, NC, 27709, USA
SOURCE: Biochemistry (2001), 40(24), 7084-7091
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The kinetic mechanisms for the inhibition of pp60c-src tyrosine kinase (Src TK) by 4-anilinoquinazolines, an important class of chems. as protein kinase inhibitors, were investigated. 4-Anilinoquinazolines with a bulky group at the 4'-position of the anilino group were shown to be competitive with both ATP and peptide, whereas mols. lacking such a bulky group only displayed an inhibition pattern typical of those competitive with ATP and noncompetitive with peptide. Modifications of the substituents on the carbocyclic ring did not perturb the inhibition pattern although the affinities of these modified inhibitors for Src TK were affected. Structural modeling of Src TK with inhibitor and peptide substrate bound indicated a direct atomic conflict between the bulky 4-position group and the hydroxy of the peptide tyrosyl to which the γ-phosphate of ATP is transferred during the kinase reaction. This atomic conflict would likely prevent

simultaneous binding of both inhibitor and peptide, consistent with the observed kinetic competitiveness of the inhibitor with peptide. The dual site inhibitors appeared to have both enhanced potency and selectivity for Src TK. One such inhibitor , 4-(4'-phenoxyanilino)-6,7-dimethoxyquinazoline, had a 15 nM potency against Src TK and was selective over receptor tyrosine kinases VEGFR2 by 88-fold and C-fms by 190-fold.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 14 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:354377 CAPLUS Full-text
DOCUMENT NUMBER: 135:146994
TITLE: Indolinone tyrosine kinase inhibitors block Kit activation and growth of small-cell lung cancer cells
AUTHOR(S): Krystal, Geoffrey W.; Honsawek, Sittisak; Kiewlich, David; Liang, Congxin; Vasile, Stefan; Sun, Li; McMahon, Gerald; Lipson, Kenneth E.
CORPORATE SOURCE: Departments of Internal Medicine and Microbiology/Immunology, McGuire Veterans Affairs Medical Center, Virginia Commonwealth University, Richmond, VA, 23249, USA
SOURCE: Cancer Research (2001), 61(9), 3660-3668
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Six indolinone tyrosine kinase inhibitors were characterized for their ability to inhibit Kit kinase and for their effects on the growth of small-cell lung cancer (SCLC) cell lines. All six compds. were potent inhibitors of Kit kinase in a biochem. assay. A homol. model of compound binding to the ATP -binding site could account for the increased potency caused by the addition of a propionate moiety to the indolinone core but not that caused by addition of a chloride moiety. Although all of the compds. tested were potent in the biochem. assay, several exhibited significantly less potency in cellular kinase assays. Their effects on stem cell factor (SCF)-dependent Kit autophosphorylation and SCLC cell growth were also examined Inhibition of SCF-stimulated Kit activation and cell growth of the H526 cell line was concentration dependent. At concns. that inhibited SCF-stimulated H526 cell growth, there was little effect on insulin-like growth factor-1-stimulated growth, suggesting that these compds. exhibit reasonable selectivity for inhibition of Kit-mediated proliferation. Higher concns. of the compds. were needed to inhibit serum-stimulated growth. Of the six compds. examined, SU5416 and SU6597 possessed the best cellular potency and, therefore, their effect on the growth of multiple SCLC cell lines in serum-containing media was examined In addition to inhibiting proliferation, these compds. also induced cell death of several SCLC cell lines, but not of normal human diploid fibroblasts, in complete media. These observations suggest that Kit kinase inhibitors such as these may offer a new approach for inhibiting Kit-mediated proliferation of tumors such as SCLC, gastrointestinal stromal tumors, seminomas, and leukemias.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 15 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:322616 CAPLUS Full-text
DOCUMENT NUMBER: 135:56192
TITLE: An RGD sequence in the P2Y2 receptor interacts with αVβ3 integrins and is required for Go-mediated signal transduction
AUTHOR(S): Erb, Laurie; Liu, Jun; Ockerhausen, Jonathan; Kong, Qiongman; Garrad, Richard C.; Griffin, Korey; Neal, Chris; Krugh, Brent; Santiago-Perez, Laura I.; Gonzalez, Fernando A.; Gresham, Hattie D.; Turner, John T.; Weisman, Gary A.
CORPORATE SOURCE: Department of Biochemistry, University of Missouri-Columbia, Columbia, MO, 65212, USA
SOURCE: Journal of Cell Biology (2001), 153(3), 491-501
CODEN: JCLBA3; ISSN: 0021-9525
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The P2Y2 nucleotide receptor (P2Y2R) contains the integrin-binding domain arginine-glycine-aspartic acid (RGD) in its first extracellular loop, raising the possibility that this G protein-coupled receptor interacts directly with an integrin. Binding of a peptide corresponding to the first extracellular loop of the P2Y2R to K562 erythroleukemia cells was inhibited by antibodies against αVβ3/β5 integrins and the integrin-associated thrombospondin receptor, CD47. Immunofluorescence of cells transfected with epitope-tagged P2Y2Rs indicated that αV integrins colocalized 10-fold better with the wild-type P2Y2R than with a mutant P2Y2R in which the RGD sequence was replaced with RGE. Compared with the wild-type P2Y2R, the RGE mutant required 1000-fold higher agonist concns. to phosphorylate focal adhesion kinase, activate extracellular signal-

regulated kinases, and initiate the PLC-dependent mobilization of intracellular Ca2+. Furthermore, an anti-αV integrin antibody partially inhibited these signaling events mediated by the wild-type P2Y2R. Pertussis toxin, an inhibitor of Gi/o proteins, partially inhibited Ca2+ mobilization mediated by the wild-type P2Y2R, but not by the RGE mutant, suggesting that the RGD sequence is required for P2Y2R-mediated activation of Go, but not Gq. Since CD47 has been shown to associate directly with Gi/o family proteins, these results suggest that interactions between P2Y2Rs, integrins, and CD47 may be important for coupling the P2Y2R to Go.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 16 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:320376 CAPLUS Full-text
DOCUMENT NUMBER: 135:92605
TITLE: Soluble 2-Substituted Aminopyrido[2,3-d]pyrimidin-7-yl Ureas. Structure-Activity Relationships against Selected Tyrosine Kinases and Exploration of in Vitro and in Vivo Anticancer Activity
AUTHOR(S): Schroeder, Mel C.; Hamby, James M.; Connolly, Cleo J. C.; Grohar, Patrick J.; Winters, R. Thomas; Barvian, Mark R.; Moore, Charles W.; Boushelle, Stacey L.; Crean, Sheila M.; Kraker, Alan J.; Driscoll, Denise L.; Vincent, Patrick W.; Elliott, William L.; Lu, Gina H.; Batley, Brian L.; Dahring, Tawny K.; Major, Terry C.; Panek, Robert L.; Doherty, Annette M.; Showalter, H. D. Hollis
CORPORATE SOURCE: Departments of Chemistry Cancer Research and Vascular and Cardiac Diseases, Pfizer Global Research & Development Ann Arbor Laboratories, Ann Arbor, MI, 48105, USA
SOURCE: Journal of Medicinal Chemistry (2001), 44(12), 1915-1926
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 135:92605
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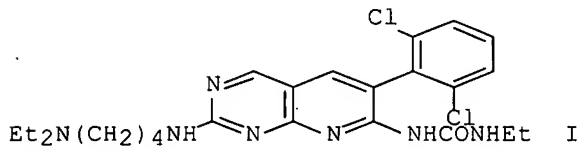

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AB In a search for medicinal agents to treat proliferative diseases, 2-substituted aminopyrido[2,3-d]pyrimidin-7-ylureas were discovered as a novel class of soluble, potent, broadly active tyrosine kinase (TK) inhibitors. An efficient route was developed that enabled the synthesis of a wide variety of analogs with substitution on several positions of the template. From the lead structure, 1-[2-amino-6-(2,6- dichlorophenyl)pyrido[2,3-d]pyrimidin-2-yl]-3-tert.-butylurea , several series of analogs were made that examined the C-6 aryl substituent, a variety of water solubilizing substituents at the C-2 position, and urea or other acyl functionality at the N-7 position. Compds. of this series were competitive with ATP and displayed submicromolar to low nanomolar potency against a panel of TKs, including receptor (platelet-derived growth factor, PDGFr; fibroblast growth factor, FGFr;) and non-receptor (c-Src) classes. Several of the most potent compds. displayed submicromolar inhibition of PDGF-mediated receptor autophosphorylation in rat aortic vascular smooth muscle cells and low micromolar inhibition of cellular growth in five human tumor cell lines. One of the more thoroughly evaluated members, I, with IC50 values of 0.21 μM (PDGFr), 0.049 μM (bFGFr), and 0.018 μM (c-Src), was evaluated in in vivo studies against a panel of five human tumor xenografts, with known and/or inferred dependence on the EGFr, PDGFr, and c-Src TKs. I produced a tumor growth delay of 14 days against the Colo-205 colon xenograft model.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 17 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:61042 CAPLUS Full-text
DOCUMENT NUMBER: 134:246874

TITLE: Indirubins inhibit glycogen synthase kinase -3β and CDK5/P25, two protein kinases involved in abnormal tau phosphorylation in Alzheimer's disease. A property common to most cyclin-dependent kinase inhibitors ?

AUTHOR(S): Leclerc, Sophie; Garnier, Matthieu; Hoessel, Ralph; Marko, Doris; Bibb, James A.; Snyder, Gretchen L.; Greengard, Paul; Biernat, Jacek; Wu, Yong-Zhong; Mandelkow, Eva-Maria; Eisenbrand, Gerhard; Meijer, Laurent

CORPORATE SOURCE: CNRS, Cell Cycle Group, Station Biologique, Roscoff, 29682, Fr.

SOURCE: Journal of Biological Chemistry (2001), 276(1), 251-260
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The bis-indole indirubin is an active ingredient of Danggui Longhui Wan, a traditional Chinese medicine recipe used in the treatment of chronic diseases such as leukemias. The antitumoral properties of indirubin appear to correlate with their antimitotic effects. Indirubins were recently described as potent (IC50: 50-100 nM) inhibitors of cyclin-dependent kinases (CDKs). We report here that indirubins are also powerful inhibitors (IC50: 5-50 nM) of an evolutionarily related kinase, glycogen synthase kinase -3β (GSK-3β). Testing of a series of indoles and bis-indoles against GSK-3β, CDK1/cyclin B, and CDK5/p25 shows that only indirubins inhibit these kinases. The structure- activity relationship study also suggests that indirubins bind to GSK-3β's ATP binding pocket in a way similar to their binding to CDKs, the details of which were recently revealed by crystallog. anal. GSK-3β, along with CDK5, is responsible for most of the abnormal hyperphosphorylation of the microtubule-binding protein tau observed in Alzheimer's disease. Indirubin-3'-monoxime inhibits tau phosphorylation in vitro and in vivo at Alzheimer's disease-specific sites. Indirubins may thus have important implications in the study and treatment of neurodegenerative disorders. Indirubin-3'-monoxime also inhibits the in vivo phosphorylation of DARPP-32 by CDK5 on Thr-75, thereby mimicking one of the effects of dopamine in the striatum. Finally, we show that many, but not all, reported CDK inhibitors are powerful inhibitors of GSK-3β. To which extent these GSK-3β effects of CDK inhibitors actually contribute to their antimitotic and antitumoral properties remains to be determined Indirubins constitute the first family of low nanomolar inhibitors of GSK-3β to be described.

REFERENCE COUNT: 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 18 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:55541 CAPLUS Full-text

DOCUMENT NUMBER: 134:260864

TITLE: Synthesis and Src kinase inhibitory activity of a series of 4-phenylamino-3-quinolinecarbonitriles

AUTHOR(S): Boschelli, Diane H.; Wang, Yanong D.; Ye, Fei; Wu, Biqi; Zhang, Nan; Dutia, Minu; Powell, Dennis W.; Wissner, Allan; Arndt, Kim; Weber, Jennifer M.; Boschelli, Frank

CORPORATE SOURCE: Chemical Sciences and Oncology, Wyeth-Ayerst Research, Pearl River, NY, 10965, USA

SOURCE: Journal of Medicinal Chemistry (2001), 44(5), 822-833
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 134:260864

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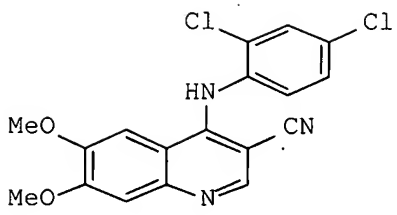

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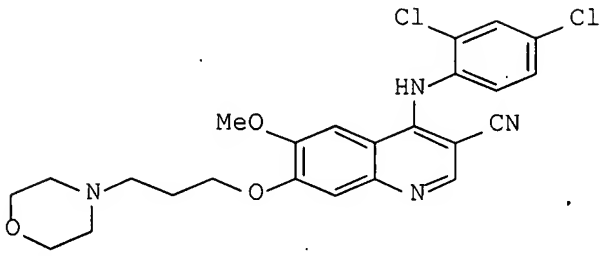


II

AB Screening of a directed compound library in a yeast-based assay identified 4-[(2,4-dichlorophenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile (I) as a Src inhibitor. An enzymic assay established that I was an ATP-competitive inhibitor of the kinase activity of Src. We present here SAR data for I which shows that the aniline group at C-4, the carbonitrile group at C-3, and the alkoxy groups at C-6 and C-7 of the quinoline are crucial for optimal activity. Increasing the size of the C-2 substituent of the aniline at C-4 of I from chloro to bromo to iodo resulted in a corresponding increase in Src inhibition. Furthermore, replacement of the 7-methoxy group of I with various 3-heteroalkylaminopropoxy groups provided increased inhibition of both Src enzymic and cellular activity. Compound II, which contains a 3-morpholinopropoxy group, had an IC50 of 3.8 nM in the Src enzymic assay and an IC50 of 940 nM for the inhibition of Src-dependent cell proliferation.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 19 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:901175 CAPLUS Full-text

DOCUMENT NUMBER: 134:172694

TITLE: Direct Inhibition of the Hexose Transporter GLUT1 by Tyrosine Kinase Inhibitors

AUTHOR(S): Vera, Juan Carlos; Reyes, Alejandro M.; Velasquez, Fernando V.; Rivas, Coralia I.; Zhang, Rong Hua; Strobel, Pablo; Slebe, Juan Carlos; Nunez-Alarcon, Juana; Golde, David W.

CORPORATE SOURCE: Program in Molecular Pharmacology and Therapeutics, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA

SOURCE: Biochemistry (2001), 40(3), 777-790
CODEN: BICHAW; ISSN: 0006-2960

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The facilitative hexose transporter GLUT1 is a multifunctional protein that transports hexoses and dehydroascorbic acid, the oxidized form of vitamin C, and interacts with several mols. structurally unrelated to the transported substrates. Here we analyzed in detail the interaction of GLUT1 with a group of tyrosine kinase inhibitors that include natural products of the family of flavones and isoflavones and synthetic compds. such as the tyrphostins. These compds. inhibited, in a dose-dependent manner, the transport of hexoses and dehydroascorbic acid in human myeloid HL-60 cells, in transfected Chinese hamster ovary cells overexpressing GLUT1, and in normal human erythrocytes, and blocked the glucose-displaceable binding of cytochalasin B to GLUT1 in erythrocyte ghosts. Kinetic anal. of transport data indicated that only tyrosine kinase inhibitors with specificity for ATP binding sites inhibited the transport activity of GLUT1 in a competitive manner. In contrast, those inhibitors that are competitive with tyrosine but not with ATP failed to inhibit hexose uptake or did so in a noncompetitive manner. These results, together with recent evidence demonstrating that GLUT1 is a nucleotide binding protein, support the concept that the inhibitory effect on transport is related to the direct interaction of the inhibitors with GLUT1. We conclude that predicted nucleotide-binding motifs present in GLUT1 are important for the interaction of the tyrosine kinase inhibitors with the transporter and may participate directly in the binding transport of substrates by GLUT1.

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 20 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:892728 CAPLUS Full-text
DOCUMENT NUMBER: 134:187919
TITLE: Crystal structure of human cyclin-dependent kinase 2 in complex with the adenine-derived inhibitor H717
AUTHOR(S): Dreyer, Matthias K.; Borcherding, David R.; Dumont, Jennifer A.; Peet, Norton P.; Tsay, Joseph T.; Wright, Paul S.; Bitonti, Alan J.; Shen, Jian; Kim, Sung-Hou
CORPORATE SOURCE: Department of Chemistry and Lawrence Berkeley National Laboratory, University of California, Berkeley, CA, 94720, USA
SOURCE: Journal of Medicinal Chemistry (2001), 44(4), 524-530
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cyclin-dependent kinases (CDKs) are regulatory proteins of the eukaryotic cell cycle. They act after association with different cyclins, the concns. of which vary throughout the progression of the cell cycle. As central mediators of cell growth, CDKs are potential targets for inhibitory mols. that would allow disruption of the cell cycle in order to evoke an antiproliferative effect and may therefore be useful as cancer therapeutics. We synthesized several inhibitory 2,6,9-trisubstituted purine derivs. and solved the crystal structure of one of these compds., H717, in complex with human CDK2 at 2.6 Å resolution The orientation of the C2-p-diaminocyclohexyl portion of the inhibitor is strikingly different from those of similar moieties in other related inhibitor complexes. The N9-cyclopentyl ring fully occupies a space in the enzyme which is otherwise empty, while the C6-N-aminobenzyl substituent points out of the ATP-binding site. The structure provides a basis for the further development of more potent inhibitory drugs.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 21 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:883011 CAPLUS Full-text
DOCUMENT NUMBER: 134:336046
TITLE: De novo design of inhibitors of protein tyrosine kinase pp60c-src
AUTHOR(S): Langer, Thierry; Konig, Matthias A.; Schischkow, Georg; Guccione, Salvatore
CORPORATE SOURCE: Institute of Pharmaceutical Chemistry, University of Innsbruck, Innsbruck, A-6020, Austria
SOURCE: Molecular Modeling and Prediction of Bioactivity, [Proceedings of the European Symposium on Quantitative Structure-Activity Relationships: Molecular Modeling and Prediction of Bioactivity], 12th, Copenhagen, Denmark, Aug. 23-28, 1998 (2000), Meeting Date 1998, 361-362. Editor(s): Gundertofte, Klaus; Jorgensen, Flemming Steen. Kluwer Academic/Plenum Publishers: New York, N. Y.
CODEN: 69ASO3
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Protein tyrosine kinase (PTK) pp60c-src is a new and promising target for the modulation of cell proliferation. In order to find new specific inhibitors for this enzyme, a two-step computer-aided ligand design study was conducted. First, a 3D QSAR model based on a training set of 25 known ligands was established using the comparative mol. field anal. (CoMFA) approach. Second, a de novo approach using the x-ray coordinates of human PTK pp60c-src was applied using the LUDI software tool.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 22 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:792832 CAPLUS Full-text
DOCUMENT NUMBER: 134:127686
TITLE: Pyrido[2,3-d]pyrimidin-7-one Inhibitors of Cyclin-Dependent Kinases
AUTHOR(S): Barvian, Mark; Boschelli, Dianne; Cossrow, Jennifer; Dobrusin, Ellen; Fattaey, Ali; Fritsch, Alex; Fry, David; Harvey, Patricia; Keller, Paul; Garrett, Michelle; La, Frances; Leopold, Wilbur; McNamara, Dennis; Quin, Marie; Trumpp-Kallmeyer, Susanne; Toogood, Peter; Wu, Zhipei; Zhang, Erli
CORPORATE SOURCE: Departments of Chemistry and Cancer Research, Parke-Davis Pharmaceutical Research Division of Warner Lambert Company, Ann Arbor, MI, 48105, USA

SOURCE: Journal of Medicinal Chemistry (2000), 43(24), 4606-4616
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:127686

AB The identification of 8-ethyl-2-phenylamino-8H-pyrido[2,3-d]pyrimidin-7- one as an inhibitor of Cdk4 led to the initiation of a program to evaluate related pyrido[2,3-d]pyrimidin-7-ones for inhibition of cyclin-dependent kinases (Cdks). Anal. of more than 60 analogs has identified some clear SAR trends that may be exploited in the design of more potent Cdk inhibitors. The most potent Cdk4 inhibitors reported in this study inhibit Cdk4 with IC50 = 0.004 μM ([ATP] = 25 μM). X-ray crystallog. anal. of representative compds. bound to the related kinase, Cdk2, reveals that they occupy the ATP binding site. Modest selectivity between Cdks is exhibited by some compds., and Cdk4-selective inhibitors block pRb+ cells in the G1-phase of the cell division cycle.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 23 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:783388 CAPLUS Full-text
DOCUMENT NUMBER: 134:95109
TITLE: Structural determinants of phosphoinositide 3-kinase inhibition by wortmannin, LY294002, quercetin, myricetin, and staurosporine
AUTHOR(S): Walker, Edward H.; Pacold, Michael E.; Perisic, Olga; Stephens, Len; Hawkins, Philip T.; Wymann, Matthias P.; Williams, Roger L.
CORPORATE SOURCE: MRC Laboratory of Molecular Biology, MRC Centre, Cambridge, CB2 2QH, UK
SOURCE: Molecular Cell (2000), 6(4), 909-919
CODEN: MOCEFL; ISSN: 1097-2765
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The specific phosphoinositide 3-kinase (P13K) inhibitors wortmannin and LY294002 have been invaluable tools for elucidating the roles of these enzymes in signal transduction pathways. The X-ray crystallog. structures of P13K bound to these lipid kinase inhibitors and to the broad-spectrum protein kinase inhibitors quercetin, myricetin, and staurosporine reveal how these compds. fit into the ATP binding pocket. With a nanomolar IC50, wortmannin most closely fits and fills the active site and induces a conformational change in the catalytic domain. Surprisingly, LY294002 and the lead compound on which it was designed, quercetin, as well as the closely related flavonoid myricetin bind P13K in remarkably different orientations that are related to each other by 1800 rotations. Staurosporine/P13K interactions are reminiscent of low-affinity protein kinase/staurosporine complexes. These results provide a rich basis for development of isoform-specific P13K inhibitors with therapeutic potential.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 24 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:727124 CAPLUS Full-text
DOCUMENT NUMBER: 134:50984
TITLE: 3D-QSAR CoMFA on Cyclin-Dependent Kinase Inhibitors
AUTHOR(S): Ducrot, Pierre; Legraverend, Michel; Grierson, David S.
CORPORATE SOURCE: Section de Recherche, Institut Curie UMR 176 CNRS, Orsay, 91405, Fr.
SOURCE: Journal of Medicinal Chemistry (2000), 43(22), 4098-4108
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Several series of cyclin-dependent kinase inhibitors previously prepared in our laboratory were compared using 3D-QSAR (CDK1) and docking (CDK2) techniques. Evaluation of our own library of 93 purine derivs. served to establish the model which was validated by evaluation of an external library of 71 compds. The best predictions were obtained with the CoMFA standard model (q2 = 0.68, r2 = 0.90) and with the CoMSIA combined steric, electrostatic, and lipophilic fields (q2 = 0.74, r2 = 0.90). The CDK1 3D-QSAR model was then superimposed to the ATP/CDK2 binding site, giving direct contour maps of the different fields. Although too few compds. were evaluated on CDK5 to derive a 3D-QSAR model, some interesting SARs have been deduced. Comparison of the results obtained from both methods helped with understanding the specific activity of some compds. and designing new specific CDK inhibitors.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 25 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:718482 CAPLUS Full-text
DOCUMENT NUMBER: 134:50976
TITLE: Classification of Kinase Inhibitors Using BCUT Descriptors
AUTHOR(S): Pirard, Bernard; Pickett, Stephen D.
CORPORATE SOURCE: Aventis Pharma, Dagenham Research Centre, Dagenham Essex, RM10 7XS, UK
SOURCE: Journal of Chemical Information and Computer Sciences (2000), 40(6), 1431-1440
CODEN: JCISD8; ISSN: 0095-2338
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB BCUTs are an interesting class of mol. descriptor which have been proposed for a number of design and QSAR type tasks. It is important to understand what kind of information any particular descriptor encodes and to be able to relate this to the biol. properties of the mols. In this paper the authors present studies with BCUTs for the classification of ATP site directed kinase inhibitors active against five different protein kinases: three from the serine/threonine family and two from the tyrosine kinase family. In combination with a chemometric method, PLS discriminant anal., the BCUTs are able to correctly classify the ligands according to their target. A novel class of kinase inhibitors is correctly predicted as inhibitors of the EGFR tyrosine kinase. Comparison with other descriptor types such as two-dimensional fingerprints and three-dimensional pharmacophore-based descriptors allows the authors to gain an insight into the level of information contained within the BCUTs.
REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 26 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:459471 CAPLUS Full-text
DOCUMENT NUMBER: 133:216721
TITLE: Structure-based design modifications of the paullone molecular scaffold for cyclin-dependent kinase inhibition
AUTHOR(S): Gussio, Rick; Zaharevitz, Daniel W.; McGrath, Connor F.; Pattabiraman, Nagarajan; Kellogg, Glen E.; Schultz, Christiane; Link, Andreas; Kunick, Conrad; Leost, Maryse; Meijer, Laurent; Sausville, Edward A.
CORPORATE SOURCE: Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Frederick, MD, 21702, USA
SOURCE: Anti-Cancer Drug Design (2000), 15(1), 53-66
CODEN: ACDDEA; ISSN: 0266-9536
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A congeneric series of paullones were characterized using a 3-D QSAR with cyclin-dependent kinase 1 (CDK1) inhibition data. A homol. model of CDK1-cyclin B was developed from the crystal structure of CDK2-cyclin A, which subsequently served as the basis for the structure-based design. Paullones were docked into the ATP binding site of the CDK1-cyclin B models and were optimized with mol. mechanics. Hydropathic analyses of the paullone-CDK1 complexes were performed after the atom types were assigned based on each ligand's electronic properties calculated from quantum mechanics. Hydropathic descriptors formed a significant multiple regression equation that predicts paullone IC50 data. The results indicate that the combination of hydropathic descriptors with mol. mechanics geometries are sufficient to design overt steric and chemical complementarity of the ligands. However, the electronic properties derived from quantum mechanics helped direct synthetic chemical efforts to produce ligands that promote better charge transfer and strengthen hydrogen bonding as facilitated by resonance stabilization. Compds. with low affinity for CDK1 were poor charge acceptors and made less than ideal hydrogen bonding arrangements with the receptor. These considerations led to the prediction that structures such as 9-cyanopaullone would be considerably more potent than the parent compound, a finding supported by enzyme inhibition data. Also, 9-nitropaullone emerged as a paullone which also had similar potency in enzyme inhibition as well as a favorable anti-proliferative activity profile in living cells.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 27 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:367303 CAPLUS Full-text
DOCUMENT NUMBER: 133:173847
TITLE: Docking-Based Development of Purine-like Inhibitors of Cyclin-Dependent Kinase -2
AUTHOR(S): Otyepka, Michal; Krystof, Vladimir; Havlicek, Libor; Siglerova, Vera; Strnad, Miroslav; Koca, Jaroslav

CORPORATE SOURCE: Department of Inorganic and Physical Chemistry, Faculty of Science, Palacky University, Olomouc, 771 46, Czech Rep.
SOURCE: Journal of Medicinal Chemistry (2000), 43(13), 2506-2513
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The cell division cycle is controlled by cyclin-dependent kinases (cdk), which consist of a catalytic subunit (cdk1-cdk8) and a regulatory subunit (cyclin A-H). Purine-like inhibitors of cyclin-dependent kinases have recently been found to be of potential use as anticancer drugs. Rigid and flexible docking techniques were used for anal. of binding mode and design of new inhibitors . X-ray structures of three (ATP, olomoucine, roscovitine) cdk2 complexes were available at the beginning of the study and were used to optimize the docking parameters. The new potential inhibitors were then docked into the cdk2 enzyme, and the enzyme/inhibitor interaction energies were calculated and tested against the assayed activities of cdk1 (37 compds.) and cdk2 (9 compds.). A significant rank correlation between the activity and the rigid docking interaction energy has been found. This implies that (i) the rigid docking can be used as a tool for qual. prediction of activity and (ii) values obtained by the rigid docking technique into the cdk2 active site can also be used for the prediction of cdk1 activity. While the resulting geometries obtained by the rigid docking are in good agreement with the x-ray data, the flexible docking did not always produce the same inhibitor conformation as that found in the crystal.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 28 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:331908 CAPLUS Full-text
TITLE: Design, synthesis, and biological evaluation of O6-alkylguanine and O4-alkylpyrimidine cyclin-dependent kinase inhibitors
AUTHOR(S): Griffin, Roger J.; Arris, Christine E.; Calvert, A. Hilary; Curtin, Nicola J.; Jewsbury, Phillip; Endicott, Jane A.; Gibson, Ashleigh E.; Boyle, F. Tom; Golding, Bernard T.; Grant, Sharon; Johnson, Louise N.; Noble, Martin E. M.; Newell, David R.; Lawrie, Alison
CORPORATE SOURCE: Dept of Chemistry, University of Newcastle upon Tyne, Newcastle upon Tyne, UK
SOURCE: Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000 (2000), MEDI-296. American Chemical Society: Washington, D. C.
CODEN: 69CLAC
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

AB Inhibitors of cyclin dependent kinases (CDKs) are potentially useful as cancer therapeutic agents, and as probes for studying cell cycle regulation. Novel O6-alkylpurines and O4-alkylpyrimidines have been synthesized and evaluated as inhibitors of starfish CDK1/cyclin B and human CDK2/cyclin A. NU2058 (1; Ki values=CDK1 5 ± 1 μM, CDK2 12 ± 3 μM) and NU6027 (2; Ki values=CDK1 2.5 ± 0.4 μM, CDK2 1.3 ± 0.2 μM) were shown to be competitive inhibitors with respect to ATP. The structures of a number of CDK2/inhibitor complexes have been determined by X-ray crystallog., and reveal novel inhibitor-protein interactions. The crystal structure-based design, synthesis and biol. evaluation of these series of inhibitors will be discussed, and structure-activity relationships will be presented.

L7 ANSWER 29 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:219301 CAPLUS Full-text
DOCUMENT NUMBER: 133:39765
TITLE: Cyclic Peptides Incorporating 4-Carboxyphenylalanine and Phosphotyrosine Are Potent Inhibitors of pp60c-src
AUTHOR(S): Wang, Wei; Ramdas, Latha; Sun, Gongqin; Ke, Shi; Obeyesekere, Nihal U.; Budde, Raymond J. A.; McMurray, John S.
CORPORATE SOURCE: Department of Neuro-Oncology, University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Biochemistry (2000), 39(17), 5221-5228
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The protein tyrosine kinase, pp60c-src, is involved in cellular signaling and is activated during mitosis and in various tumors. We have been employing cyclic decapeptides to identify the

determinants for substrate binding and phosphorylation to develop inhibitors competitive with protein substrates of Src. A structure- activity study revealed that, at the position 3 residues C-terminal to the phosphorylated tyrosine (Y + 3), both glutamic acid and phenylalanine gave identical Ki, Km, and Vmax values. We hypothesized that the area of Src that binds the Y + 3 residue contains either a pos. charged lysine or an arginine, capable of ionic interactions with glutamic acid or cation-π interactions with phenylalanine. To test this hypothesis, a series of phenylalanine analogs were substituted at position 7 (the Y + 3 residue) in cyclo(Asp1-Asn2-Glu3-Tyr4-Ala5-Phe6-Phe7-Gln8-D- Phe9-Pro10). Of these, 4-carboxyphenylalanine (4-Cpa) and phosphotyrosine resulted in high affinity peptides exhibiting Ki values of 0.85 and 1.1 μM, resp., 180- and 130-fold increases in potency over the parent cyclic peptide (Ki = 150 μM). These peptides were noncompetitive with respect to ATP and competitive against the phosphate-accepting substrate, polyGlu4Tyr. The truncated cyclic peptide, cyclo(Phe-4-Cpa-Gln-D-Phe-Pro-Asp-Aca) (Aca = ε-aminocaproic acid), which did not contain tyrosine, was also a competitive inhibitor with a Ki value of 24 μM. We conclude that these cyclic peptides bind to a pos. charged area that is near the phosphate transfer region of the active site of Src but does not necessarily include the tyrosine-binding pocket. Furthermore, the 4-Cpa-containing cyclic decapeptide shows remarkable selectivity in the inhibition of Src vs. the src family members Yes and Lck, as well as other protein tyrosine kinases, Ser/Thr kinases, and other ATP -utilizing enzymes.

REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 30 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:208759 CAPLUS Full-text
DOCUMENT NUMBER: 132:303131
TITLE: The design, synthesis and activity of non-ATP competitive inhibitors of pp60c-src tyrosine kinase. Part 2. Hydroxyindole derivatives
AUTHOR(S): Milkiewicz, Karen L.; Marsilje, Thomas H.; Woodworth, Richard P., Jr.; Bifulco, Neil., Jr.; Hangauer, Matthew J.; Hangauer, David G.
CORPORATE SOURCE: Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, NY, 14260-1200, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2000), 10(5), 483-486
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB As part of a continuing effort to identify novel scaffolds that inhibit the pp60c-src protein tyrosine kinase, a series of hydroxyindole amides was rationally designed and synthesized (no data). The most potent derivative was found to bind non-competitively with respect to ATP.
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 31 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:208758 CAPLUS Full-text
DOCUMENT NUMBER: 132:303130
TITLE: The design, synthesis and activity of non-ATP competitive inhibitors of pp60c-src tyrosine kinase. Part 1. Hydroxynaphthalene derivatives
AUTHOR(S): Marsilje, Thomas H.; Milkiewicz, Karen L.; Hangauer, David G.
CORPORATE SOURCE: Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, NY, 14260-1200, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2000), 10(5), 477-481
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of hydroxynaphthalene pp60c-src non-peptide inhibitors was designed, using the crystal structure of the insulin receptor tyrosine kinase as a qual. model, to target the peptide substrate binding site. Representative inhibitors were shown to bind non-competitively with respect to ATP.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 32 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:164843 CAPLUS Full-text
DOCUMENT NUMBER: 132:317628
TITLE: Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal

growth factor receptor: 4-(Phenylamino)quinazoline- and 4-(Phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides bearing additional solubilizing functions

AUTHOR(S): Smaill, Jeff B.; Rewcastle, Gordon W.; Loo, Joseph A.; Greis, Kenneth D.; Chan, O. Helen; Reyner, Eric L.; Lipka, Elke; Showalter, H. D. Hollis; Vincent, Patrick W.; Elliott, William L.; Denny, William A.

CORPORATE SOURCE: Auckland Cancer Society Research Centre Faculty of Medical and Health Sciences, The University of Auckland, Auckland, N. Z.

SOURCE: Journal of Medicinal Chemistry (2000), 43(7), 1380-1397
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB 4-Anilinoquinazoline- and 4-anilinopyrido[3,2-d]pyrimidine-6-acrylamides substituted with solubilizing 7-alkylamine or 7-alkoxyamine side chains were prepared by reaction of the corresponding 6-amines with acrylic acid or acrylic acid anhydrides. In the pyrido[3,2-d]pyrimidine series, the intermediate 6-amino-7-alkylamines were prepared from 7-bromo-6-fluoropyrido[3,2-d]pyrimidine via Stille coupling with the appropriate stannane under palladium(0) catalysis. This proved a versatile method for the introduction of cationic solubilizing side chains. The compds. were evaluated for their inhibition of phosphorylation of the isolated EGFR enzyme and for inhibition of EGF-stimulated autophosphorylation of EGFR in A431 cells and of heregulin-stimulated autophosphorylation of erbB2 in MDA-MB 453 cells. Quinazoline analogs with 7-alkoxyamine solubilizing groups were potent irreversible inhibitors of the isolated EGFR enzyme, with IC50[app] values from 2 to 4 nM, and potently inhibited both EGFR and erbB2 autophosphorylation in cells. 7-Alkylamino- and 7-alkoxyaminopyrido[3,2-d]pyrimidines were also irreversible inhibitors with equal or superior potency against the isolated enzyme but were less effective in the cellular autophosphorylation assays. Both quinazoline- and pyrido[3,2-d]pyrimidine-6-acrylamides bound at the ATP site alkylating cysteine 773, as shown by electrospray ionization mass spectrometry, and had similar rates of absorptive and secretory transport in Caco-2 cells. A comparison of two 7-propoxymorpholide analogs showed that the pyrido[3,2-d]pyrimidine-6- acrylamide had greater amide instability and higher acrylamide reactivity, being converted to glutathione adducts in cells more rapidly than the corresponding quinazoline. This difference may contribute to the observed lower cellular potency of the pyrido[3,2-d]pyrimidine-6-acrylamides. Selected compds. showed high in vivo activity against A431 xenografts on oral dosing, with the quinazolines being superior to the pyrido[3,2-d]pyrimidines. Overall, the quinazolines proved superior to previous analogs in terms of aqueous solubility, potency, and in vivo antitumor activity, and one example (CI 1033) has been selected for clin. evaluation.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 33 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:161781 CAPLUS Full-text

DOCUMENT NUMBER: 132:331230

TITLE: Cyclin-Dependent Kinase Inhibition by New C-2 Alkynylated Purine Derivatives and Molecular Structure of a CDK2-Inhibitor Complex

AUTHOR(S): Legraverend, Michel; Tunnah, Paul; Noble, Martin; Ducrot, Pierre; Ludwig, Odile; Grierson, David S.; Leost, Maryse; Meijer, Laurent; Endicott, Jane

CORPORATE SOURCE: Section de Recherche Institut Curie, UMR 176 CNRS, Orsay, 91405, Fr.

SOURCE: Journal of Medicinal Chemistry (2000), 43(7), 1282-1292
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 132:331230

AB A new series of 2,6,9-trisubstituted purines, characterized by the presence of a common alkynyl substituent at C-2 and a range of different anilino/benzylamino groups at C-6, were synthesized. These compds. were evaluated for their capacity to inhibit cyclin-dependent kinase activity (CDK1-cyclin B) in vitro. Compds. 4e (N-6-p-Cl-benzylamino derivative) and 5e (N-6-m-Cl-anilino derivative) exhibited the strongest inhibitory activity with an IC50 of 60 nM. The structure of compound 4b (N-6-p-methoxybenzylamino derivative) in complex with human CDK2 was determined by X-ray crystallog., revealing the mol. basis of inhibition by this mol. Subsequent mol. modeling studies allowed us to rationalize the SAR observed for these compds.

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 34 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:51189 CAPLUS Full-text

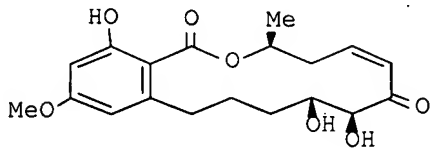
DOCUMENT NUMBER: 132:329227

TITLE: ATP site-directed competitive and irreversible inhibitors of protein kinases
AUTHOR(S): Garcia-Echeverria, Carlos; Traxler, Peter; Evans, Dean B.
CORPORATE SOURCE: Oncology Research, Novartis Pharma AG, Basel, CH-4002, Switz.
SOURCE: Medicinal Research Reviews (2000), 20(1), 28-57
CODEN: MRREDD; ISSN: 0198-6325
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 220 refs. Several tyrosine and serine/threonine protein kinases have emerged in the last few years as attractive targets in the search for new therapeutic agents being applicable in many different disease indications. Initially, inhibition of these protein kinases by ATP site-directed inhibitors was considered less prone to success, but medicinal chemists from both academia and industry have been able to impart potency and selectivity to a limited number of scaffolds by modulating and fine-tuning the interactions of the modified template with the ATP binding site of the selected kinase. The chemical templates that have been used in the synthesis of ATP site-directed protein kinase inhibitors are reviewed with emphasis on the kinase inhibitors that have entered or are about to enter clin. trials. Examples have been selected to illustrate how structure-based design approaches and new methods to increase compound diversity have had an impact on this area of research.

REFERENCE COUNT: 220 THERE ARE 220 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 35 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN.
ACCESSION NUMBER: 2000:17527 CAPLUS Full-text
DOCUMENT NUMBER: 132:191536
TITLE: Resorcylic acid lactones: naturally occurring potent and selective inhibitors of MEK
AUTHOR(S): Zhao, Annie; Lee, Seok H.; Mojena, Marina; Jenkins, Rosalind G.; Patrick, Denis R.; Huber, Hans E.; Goetz, Michael A.; Hensens, Otto D.; Zink, Deborah L.; Vilella, Dolores; Dombrowski, Anne W.; Lingham, Russell B.; Huang, Leeyuan
CORPORATE SOURCE: Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Journal of Antibiotics (1999), 52(12), 1086-1094
CODEN: JANTAJ; ISSN: 0021-8820
PUBLISHER: Japan Antibiotics Research Association
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB A resorcylic acid lactone, L-783,277 (I), isolated from a Phoma sp. (ATCC 74403) which came from the fruitbody of Helvella acetabulum, is a potent and specific inhibitor of MEK (Map kinase kinase). L-783,277 inhibits MEK with an IC50 value of 4 nM. It weakly inhibits Lck and is inactive against Raf, PKA and PKC. L-783,277 is an irreversible inhibitor of MEK and is competitive with respect to ATP. L-783,290, the trans-isomer of L-783,277, was isolated from the same culture and evaluated together with several semi-synthetic resorcylic acid lactone analogs. A preliminary structure-activity relationship is presented. Several independent cell-based assays have been carried out to study the biol. activities of these resorcylic acid lactone compds. and a brief result summary from these studies is presented.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 36 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:10975 CAPLUS Full-text
DOCUMENT NUMBER: 132:146163
TITLE: Color plates for this article are on pages 51-52.

Molecular scaffold-based design and comparison of combinatorial libraries focused on the ATP -binding site of protein kinases

AUTHOR(S): Stahura, Florence L.; Xue, Ling; Godden, Jeffrey W.; Bajorath, Jurgen

CORPORATE SOURCE: Computational Chemistry and Informatics, Bothell, WA, USA

SOURCE: Journal of Molecular Graphics & Modelling (1999), 17(1), 1-9
CODEN: JMGMFI; ISSN: 1093-3263

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Compound libraries were designed to target specifically the ATP cofactor-binding site in protein kinases by combining knowledge- and diversity-based design elements. A key aspect of the approach is the identification of mol. building blocks or scaffolds that are compatible with the binding site and therefore capture some aspects of target specificity. Scaffolds were selected on the basis of docking calcns. and anal. of known inhibitors. We have generated 75 mol. scaffolds and applied different strategies to compute diverse compds. from scaffolds or, alternatively, to screen compound databases for mols. containing these scaffolds. The resulting libraries had a similar degree of mol. diversity, with at most 12% of the compds. being identical. However, their scaffold distributions differed significantly and a small number of scaffolds dominated the majority of compds. in each library.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 37 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1999:782032 CAPLUS Full-text
Correction of: 1996:73866

DOCUMENT NUMBER: 131:351298
Correction of: 124:232395

TITLE: Tyrosine kinase inhibitors. 9. Synthesis and evaluation of fused tricyclic quinazoline analogs as ATP site inhibitors of the tyrosine kinase activity of the epidermal growth factor receptor

AUTHOR(S): Rewcastle, Gordon W.; Palmer, Brian D.; Bridges, Alexander J.; Showalter, H. D. Hollis; Sun, Li; Nelson, James; McMichael, Amy; Kraker, Alan J.; Fry, David W.; Denny, William A.

CORPORATE SOURCE: School of Medicine, University of Auckland, Auckland, 92019, N. Z.

SOURCE: Journal of Medicinal Chemistry (1996), 39(4), 918-928
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Following the discovery of 4-[(3-bromophenyl)amino]-6,7- dimethoxyquinazoline (PD 153035) as an extremely potent (IC50 0.025 nM) inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR), several fused tricyclic quinazoline analogs have been prepared and evaluated for their ability to inhibit the enzyme. The most potent compound was a linear imidazo[4,5-g]quinazoline, which exhibited an IC50 of 0.008 nM for inhibition of phosphorylation of a fragment of phospholipase C-γ1 as substrate. While N-Me analogs of linear imidazo[4,5-g]quinazolines showed similar potency, analogous N-[2-(dimethylamino)ethyl] derivs. were less effective. The next most potent compds. were linear pyrazoloquinazoline analogs (IC50 0.34 and 0.44 nM) and a pyrroloquinazoline analog (IC50 0.44 nM), while several other linear tricyclic ring systems of similar geometry to linear imidazo[4,5-g]quinazolines (triazolo-, thiazolo-, and pyrazinoquinazolines) were less effective. In the imidazo[4,5- g]quinazoline and pyrroloquinazoline series, the corresponding angular isomers were also much less effective than the linear ones. These results are consistent with structure-activity relationship studies previously developed for the 4-[(3-bromophenyl)amino]quinazolines, which suggested that small electron-donating substituents at the 6- and 7-positions were desirable for high potency. Cellular studies of a linear imidazo[4,5-g]quinazoline, i.e., N-(3-bromophenyl)-1H-imidazo[4,5-g]quinazolin-8-amine, show that it can enter cells and rapidly and very selectively shut down EGF-stimulated signal transmission by binding competitively at the ATP site of the EGFR. Following the discovery of 4-[(3-bromophenyl)amino]-6,7- dimethoxyquinazoline (PD 153035) as an extremely potent (IC50 0.025 nM) inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR), several fused tricyclic quinazoline analogs have been prepared And evaluated for their ability to inhibit the enzyme. The most potent compound was a linear imidazo[4,5-g]quinazoline, which exhibited an IC50 of 0.008 nM for inhibition of phosphorylation of a fragment of phospholipase C-γ1 as substrate. While N-Me analogs of linear imidazo[4,5-g]quinazolines showed similar potency, analogous N-[2-(dimethylamino)ethyl] derivs. were less effective. The next most potent compds. were linear pyrazoloquinazoline analogs (IC50s 0.34 and 0.44 nM) and a pyrroloquinazoline analog (IC50 0.44 nM), while several other linear tricyclic ring systems of similar geometry to linear imidazo[4,5-g]quinazolines (triazolo-, thiazolo-, and

pyrazinoquinazolines) were less effective. In the imidazo[4,5- g]quinazoline and pyrroloquinazoline series, the corresponding angular isomers were also much less effective than the linear ones. These results are consistent with structure-activity relationship studies previously developed for the 4-[(3-bromophenyl)amino]quinazolines, which suggested that small electron-donating substituents at the 6- and 7-positions were desirable for high potency. Cellular studies of a linear imidazo[4,5-g]quinazoline, i.e., N-(3-bromophenyl)-1H-imidazo[4,5-g]quinazolin-8-amine, show that it can enter cells and rapidly and very selectively shut down EGF-stimulated signal transmission by binding competitively at the ATP site of the EGFR. Following the discovery of 4-[(3-bromophenyl)amino]-6,7- dimethoxyquinazoline (PD 153035) as an extremely potent (IC50 0.025 nM) inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR), several fused tricyclic quinazoline analogs have been prepared and evaluated for their ability to inhibit the enzyme. The most potent compound was a linear imidazo[4,5-g]quinazoline, which exhibited an IC50 of 0.008 nM for inhibition of phosphorylation of a fragment of phospholipase C-γ1 as substrate. While N-Me analogs of linear imidazo[4,5-g]quinazolines showed similar potency, analogous N-[2-(dimethylamino)ethyl] derivs. were less effective. The next most potent compds. were linear pyrazoloquinazoline analogs (IC50 0.34 and 0.44 nM) and a pyrroloquinazoline analog (IC50 0.44 nM), while several other linear tricyclic ring systems of similar geometry to linear imidazo[4,5-g]quinazolines (triazolo-, thiazolo-, and pyrazinoquinazolines) were less effective. In the imidazo[4,5- g]quinazoline and pyrroloquinazoline series, the corresponding angular isomers were also much less effective than the linear ones. These results are consistent with structure-activity relationship studies previously developed for the 4-[(3-bromophenyl)amino]quinazolines, which suggested that small electron-donating substituents at the 6- and 7-positions were desirable for high potency. Cellular studies of a linear imidazo[4,5-g]quinazoline, i.e., N-(3-bromophenyl)-1H-imidazo[4,5-g]quinazolin-8-amine, show that it can enter cells and rapidly and very selectively shut down EGF-stimulated signal transmission by binding competitively at the ATP site of the EGFR. Following the discovery of 4-[(3-bromophenyl)amino]-6,7- dimethoxyquinazoline (PD 153035) as an extremely potent (IC50 0.025 nM) inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR), several fused tricyclic quinazoline analogs have been prepared and evaluated for their ability to inhibit the enzyme. The most potent compound was a linear imidazo[4,5-g]quinazoline, which exhibited an IC50 of 0.008 nM for inhibition of phosphorylation of a fragment of phospholipase C-γ1 as substrate. While N-Me analogs of linear imidazo[4,5-g]quinazolines showed similar potency, analogous N-[2-(dimethylamino)ethyl] derivs. were less effective. The next most potent compds. were linear pyrazoloquinazoline analogs (IC50s 0.34 and 0.44 nM) and a pyrroloquinazoline analog (IC50 0.44 nM), while several other linear tricyclic ring systems of similar geometry to linear imidazo[4,5-g]quinazolines (triazolo-, thiazolo-, and pyrazinoquinazolines) were less effective. In the imidazo[4,5- g]quinazoline and pyrroloquinazoline series, the corresponding angular isomers were also much less effective than the linear ones. These results are consistent with structure-activity relationship studies previously developed for the 4-[(3-bromophenyl)amino]quinazolines, which suggested that small electron-donating substituents at the 6- and 7-positions were desirable for high potency. Cellular studies of a linear imidazo[4,5-g]quinazoline, i.e., N-(3-bromophenyl)-1H-imidazo[4,5-g]quinazolin-8-amine, show that it can enter cells and rapidly and very selectively shut down EGF-stimulated signal transmission by binding competitively at the ATP site of the EGFR.

L7 ANSWER 38 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:693597 CAPLUS Full-text
DOCUMENT NUMBER: 132:30321
TITLE: Isoquinolinesulphonamide derivatives inhibit transcriptional elongation of human immunodeficiency virus type 1 RNA in a promyelocytic model of latency
AUTHOR(S): Critchfield, J. W.; Ho, O.; Roberts, B. D.; Van Lint, C.; Verdin, E.; Butera, S. T.
CORPORATE SOURCE: HIV and Retrovirology Branch, Division of AIDS, STD and TB Laboratory Research, Centers for Disease Control and Prevention, National Center for Infectious Diseases, Atlanta, GA, 30333, USA
SOURCE: Antiviral Chemistry & Chemotherapy (1999), 10(5), 275-284
CODEN: ACCHEH; ISSN: 0956-3202
PUBLISHER: International Medical Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Using the OM-10.1 promyelocytic model of inducible human immunodeficiency virus type 1 (HIV-1) infection, the authors tested a panel of known protein kinase inhibitors for an ability to block tumor necrosis factor-α-induced HIV-1 expression. Among the compds. tested, the broad-spectrum protein kinase inhibitor H-7 uniquely blocked HIV-1 expression at the level of viral transcription, but did not inhibit nuclear factor κB activation or function. In structure-activity anal. this inhibitory activity of H-7 on HIV-1 expression corresponded with the known structural requirements for the interaction of H-7 with the ATP-binding region of protein kinase C, suggesting that it was indeed related to the kinase inhibitory properties of H-7. The mechanism of H-7 transcriptional inhibition did not involve chromatin remodelling at the HIV-1 long terminal repeat promoter, as shown by nuc-1 disruption, and appeared to involve HIV-1 RNA

elongation but not initiation. Therefore, H-7 and related isoquinolinesulfonamide analogs are most likely inhibiting a kinase target essential for HIV-1 transcriptional elongation whose identity may provide new therapeutic targets for intervention.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 39 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:617691 CAPLUS Full-text
TITLE: Unique cyclin-dependent kinase (CDK) inhibitors at the ATP-site.
AUTHOR(S): Chong, Wesley K. M.; Li, Lin; Duvadie, Rohit K.; Chu, Shao Song; Yang, Y. Michelle; Nonomiya, Jim; Tucker, Kathleen D.; Knighton, Daniel R.; Ferre, Rose Ann; Lundgren, Karen; Escobar, Jorge; Minnick Price, Sharon; Huber, Andrea; Koudriakova, Tatiana; Arruda, Jeannie M.; Sisson, Wes; Aust, Robert M.; Verkhivker, Gennady M.; Schaffer, Lana; Rose, Peter W.; Lewis, Cristina T.
CORPORATE SOURCE: Medicinal Chemistry, Agouron Pharmaceuticals, Inc., San Diego, CA, 92121, USA
SOURCE: Book of Abstracts, 218th ACS National Meeting, New Orleans, Aug. 22-26 (1999), MEDI-315. American Chemical Society: Washington, D. C.
CODEN: 67ZJA5
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Control of the cell cycle could be applicable in new approaches for cancer chemotherapy. The cyclin-dependent kinases (CDK"s) and their corresponding complexes with cyclins are regulatory enzymes for which we have discovered a novel small mol. series of inhibitors, with good selectivity for the CDK"s vs. other kinases. We will discuss structure-based drug design efforts with crystal structures of complexes with CDK"s: mol. modeling channeled structure- activity relationship (SAR) efforts that achieved increased potency and led to inhibitors with various selectivity profiles, i.e., CDK4/cyclin D vs. CDK2/cyclin A or CDK1/cyclin B. Cellular effects and some preliminary examination of in vivo cancer efficacy by these inhibitors will also be addressed.

L7 ANSWER 40 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:617588 CAPLUS Full-text
TITLE: Novel ATP-site cyclin-dependent kinase (CDK) inhibitors: Selective inhibitors of CDK4/cyclin D.
AUTHOR(S): Li, Lin; Chong, Wesley K. M.; Duvadie, Rohit K.; Chu, Shao Song; Yang, Y. Michelle; Nonomiya, Jim; Tucker, Kathleen D.; Lewis, Cristina T.; Knighton, Daniel R.; Ferre, Rose Ann; Lundgren, Karen; Koudriakova, Tatiana; Escobar, Jorge; Minnick Price, Sharon; Huber, Andrea; Sisson, Wes; Aust, Robert M.; Verkhivker, Gennady M.; Schaffer, Lana; Rose, Peter W.
CORPORATE SOURCE: Medicinal Chemistry, Agouron Pharmaceuticals, Inc., San Diego, CA, 92121, USA
SOURCE: Book of Abstracts, 218th ACS National Meeting, New Orleans, Aug. 22-26 (1999), MEDI-215. American Chemical Society: Washington, D. C.
CODEN: 67ZJA5
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Intervention in the cell cycle could provide new approaches for cancer chemotherapy. The cyclin-dependent kinases (CDK"s) and their corresponding complexes with cyclin partners are key regulators--for which we have discovered a novel small mol. series of inhibitors, with potencies in the nanomolar range and good selectivity for the CDK"s vs. other kinases. The crystal structures of complexes with certain CDK"s showed these inhibitors bound in the ATP site and this information, along with mol. modeling, guided structure -activity relationship (SAR) studies that has led to selective inhibitors of CDK4/cyclin D vs. CDK2/cyclin A or CDK1/cyclin B. Cellular effects and some preliminary examination of in vivo cancer efficacy by these inhibitors will also be discussed.

L7 ANSWER 41 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:617587 CAPLUS Full-text
TITLE: Novel ATP-site cyclin-dependent kinase (CDK) inhibitors: Selective CDK inhibitors.
AUTHOR(S): Duvadie, Rohit K.; Chong, Wesley K. M.; Li, Lin; Chu, Shao Song; Yang, Y. Michelle; Nonomiya, Jim; Tucker,

Kathleen D.; Lewis, Cristina T.; Knighton, Daniel R.; Ferre, Rose Ann; Lundgren, Karen; Koudriakova, Tatiana; Escobar, Jorge; Minnick Price, Sharon; Huber, Andrea; Sisson, Wes; Aust, Robert M.; Verkhivker, Gennady M.; Schaffer, Lana; Rose, Peter W.

CORPORATE SOURCE: Medicinal Chemistry, Agouron Pharmaceuticals, Inc., San Diego, CA, 92121, USA

SOURCE: Book of Abstracts, 218th ACS National Meeting, New Orleans, Aug. 22-26 (1999), MEDI-214. American Chemical Society: Washington, D. C.
CODEN: 67ZJA5

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB A new approach to cancer chemotherapy may result from the use of modulators of the cell cycle. We will describe the discovery and evolution of a novel small mol. series that are bound in the ATP site of the cyclin-dependent kinases (CDK"s). Some of these achieved inhibition in the nanomolar range and displayed good selectivity, not affecting various other kinases. The crystal structures of complexes with certain CDK"s-- and mol. modeling-- aided structure -activity relationship (SAR) studies that yielded equipotent inhibitors of CDK1/cyclin B, CDK2/cyclin A, and CDK4/cyclin D. Selected inhibitors were examined for cellular effects and these results will be discussed.

L7 ANSWER 42 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1999:606334 CAPLUS Full-text

DOCUMENT NUMBER: 131:308298

TITLE: Kinetic study of the inhibition of CK2 by heparin fragments of different length

AUTHOR(S): O'Farrell, Fergal; Loog, Mart; Janson, Inger M.; Ek, Pia

CORPORATE SOURCE: Department of Medical Biochemistry and Microbiology, Biomedical Centre, Uppsala University, Uppsala, S-751 23, Swed.

SOURCE: Biochimica et Biophysica Acta, Protein Structure and Molecular Enzymology (1999), 1433(1-2), 68-75
CODEN: BBAEDZ; ISSN: 0167-4838

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The structure-activity relationships for the inhibition of protein kinase CK2 by heparin were investigated using purified heparin fragments of different length, varying from 4 to 24 oligosaccharide sugar units. The inhibitory potency was shown to decrease concomitant with the shortening of the heparin fragment length. The fragment of 24 oligosaccharide sugar units was the most potent inhibitor with a Ki value of 22 nM which is close to the Ki value for the com. heparin mixture available. Shortening of the heparin from 24 to 12 sugar units had a moderate influence on the inhibitory potency causing an increase in Ki values up to 151 nM while fragments shorter than 12 sugar units showed a more drastic increase in Ki values reaching up to micromolar range. The mode of inhibition was studied in respect to the protein substrate β-casein and it was shown to be competitive for the long as well as for the short heparin fragments. In contrast, the inhibition mode in respect to a synthetic peptide substrate RRRADDSDDDDD was found to be hyperbolic partial non-competitive mixed-type. Such a kinetic model suggests that heparin binds to a site on CK2 which does not overlap with the peptide substrate binding site and that a productive enzyme complex exists where both heparin and peptide substrate are simultaneously bound. This is in contrast to the competitive inhibition model of the phosphorylation of protein substrate β-casein where the binding of the protein substrate and inhibitor was mutually exclusive.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 43 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1999:591963 CAPLUS Full-text

DOCUMENT NUMBER: 131:306600

TITLE: The structure-based design of ATP-site directed protein kinase inhibitors

AUTHOR(S): Toledo, Leticia M.; Lydon, Nicholas B.; Elbaum, Daniel

CORPORATE SOURCE: Kinetix Pharmaceuticals Inc., Medford, MA, 02155, USA

SOURCE: Current Medicinal Chemistry (1999), 6(9), 775-805
CODEN: CMCHE7; ISSN: 0929-8673

PUBLISHER: Bentham Science Publishers

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 158 refs. The protein kinase family represents both a huge opportunity and a challenge for drug development. The conservation of structural features within the ATP binding cleft initially led to the belief that specificity would be difficult to achieve. This dogma has now been clearly dispelled with the discovery and clin. testing of a group of first generation compds., which are characterized by a high degree of selectivity towards a variety of oncol.

targets. The structural basis for selectivity and potency has now been clarified with the crystallization of a number of such targets in complex with inhibitors. The protein kinase inhibitor field is now ripe for the structure based exploitation of addnl. highly validated targets from a variety of therapeutic areas.

REFERENCE COUNT: 158 THERE ARE 158 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 44 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:540903 CAPLUS Full-text
TITLE: Structure-activity relationships (SAR) for human cyclin-dependent kinase 4 (CDK4)/cyclin D with novel CDK inhibitors using a CDK4 homology model.
AUTHOR(S): Schaffer, Lana; Rose, Peter W.; Chong, Wesley K. M.; Li, Lin; Duvadie, Rohit K.; Nonomiya, Jim; Knighton, Daniel R.; Ferre, RoseAnn; Yang, Y. Michelle; Chu, Shao Song; Tucker, Kathleen D.; Sisson, Wes; Aust, Robert M.; Lewis, Cristina T.
CORPORATE SOURCE: Computational Chemistry Department, Agouron Pharmaceuticals, La Jolla, CA, 92037-1022, USA
SOURCE: Book of Abstracts, 218th ACS National Meeting, New Orleans, Aug. 22-26 (1999), COMP-191. American Chemical Society: Washington, D. C.
CODEN: 67ZJA5
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Modulators of the cell cycle hold promise as new potential anticancer chemotherapeutic agents. In this regard, we have identified a novel series of small mol. inhibitors of cyclin-dependent kinases (CDK's) that bind within the ATP binding site. CDK2 and CDK4 share 45% amino acid sequence identity, and certain active site residues are different for the two kinases. The crystal structure of CDK2 was used to create a simple a homol. model for CDK4. This particular model highlighted differences between active site residues of CDK2 and CDK4 and was useful for assessing structure- activity relationships of CDK inhibitors. This model also allowed speculation about observed ligand selectivities between these two kinases. Details will also be disclosed about a protocol wherein an adapted minimization with a Generalized Born/Surface Area solvation model and the Amber force field was used to calculate the relative binding free energy differences that correlated with the apparent binding affinity (Ki) for CDK2 and CDK4.

L7 ANSWER 45 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:513708 CAPLUS Full-text
DOCUMENT NUMBER: 131:266382
TITLE: Recent advances in protein kinase inhibition: current molecular scaffolds used for inhibitor synthesis
AUTHOR(S): Stover, David R.; Lydon, Nicholas B.; Nunes, Joseph J.
CORPORATE SOURCE: Kinetix Pharmaceuticals Inc, Medford, MA, 02155, USA
SOURCE: Current Opinion in Drug Discovery & Development (1999), 2(4), 274-285
CODEN: CODDFF; ISSN: 1367-6733
PUBLISHER: Current Drugs Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 76 refs. Early efforts to discover and develop protein kinase inhibitors have focused largely on a small group of oncol. targets such as the EGFR and PKC enzymes. More recently, hundreds of protein kinases have been identified at the genetic level, many of which are now being assigned functions in a variety of signaling pathways. Addnl., mutagenesis and X-ray crystallog. studies have further defined common structural features associated with binding of the ATP cofactor within a conserved ATP binding cleft. These studies have also demonstrated significant differences in the ATP binding cleft between individual kinases, providing a mol. basis for understanding and exploiting inhibitor specificity. The current review is focused on recent developments in the field of ATP site-directed inhibitors with particular emphasis on the major scaffolds being derivatized to take advantage of variable regions of the active site.
REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 46 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:502223 CAPLUS Full-text
DOCUMENT NUMBER: 131:306738
TITLE: Benzodiazepine compounds as inhibitors of the Src protein tyrosine kinase: screening of a combinatorial library of 1,4-benzodiazepines
AUTHOR(S): Ramdas, Latha; Bunnin, Barry A.; Plunkett, Matthew J.; Sun, Gongqin; Ellman, Jonathan; Gallick, Gary; Budde,

Raymond J. A.
CORPORATE SOURCE: Department of Neuro-Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Archives of Biochemistry and Biophysics (1999), 368(2), 394-400
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We screened 1680 spatially separated compds. of a diverse combinatorial library of 1,4-benzodiazepines for their ability to inhibit the kinase activity of protein tyrosine kinases Src, Yes, Abl, Lck, Csk, and fibroblast growth factor receptor. This screening yielded novel ligands for the protein tyrosine kinase Src. In the 1,4-benzodiazepine-2-one scaffold, the preferred substituent at position R1 was 4-hydroxyphenylmethyl or a 3-indolemethyl derived from a tyrosine or tryptophan used in building the benzodiazepine, while the substituent at R2, introduced by alkylating agents, was preferably aromatic in nature. The preferred ring structure introduced on the bicyclic ring of the scaffold by acid chlorides was a p-hydroxy Ph group. The lead compound, designated as N-1-Yaa, has a 1-4-hydroxyphenylmethyl ring at R1 and a biphenylmethyl substituent at R2. The compound has an IC50 of 73 μM against Src, 2- to 6-fold lower than against other protein tyrosine kinases and >10-fold lower than against other nucleotide-utilizing enzymes. The mechanism of binding of N-1-Yaa to Src is mixed against the peptidic substrate with a Ki of 35 μM and noncompetitive against ATP-Mg with a Ki of 17 μM. Multiple inhibition anal. of the lead compound in the presence of other competitive inhibitors demonstrated that the binding of the lead compound is nonexclusive to the other competitive inhibitor. The inhibitor was found to be nontoxic to the AFB-13-human fibroblasts cells and inhibited the colony formation of HT-29 colon adenocarcinoma cells that are dependent on Src activity. (c) 1999 Academic Press.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 47 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:397258 CAPLUS Full-text
DOCUMENT NUMBER: 131:179162
TITLE: Strategies toward the design of novel and selective protein tyrosine kinase inhibitors
AUTHOR(S): Traxler, Peter; Furet, Pascal
CORPORATE SOURCE: Novartis Pharmaceuticals, Therapeutic Area Oncology, Novartis Limited, Basel, CH-4002, Switz.
SOURCE: Pharmacology & Therapeutics (1999), 82(2-3), 195-206
CODEN: PHTHDT; ISSN: 0163-7258
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 37 refs. Protein tyrosine kinases play a fundamental role in signal transduction pathways. Deregulated tyrosine kinase activity has been observed in many proliferative diseases (e.g., cancer, psoriasis, restenosis, etc.). Tyrosine kinases are, therefore, attractive targets for the design of new therapeutic agents against cancer. We have built up a pharmacophore model of the ATP-binding site of the epidermal growth factor receptor (EGFR) kinase and used it for the rational design of kinase inhibitors. Several examples of the successful use of this model are presented in this review. Amongst these, 4-substituted-pyrrolo[2,3- d]pyrimidines, a new class of highly potent and selective inhibitors of the EGFR kinase, have been identified and further optimized. The most active derivs. inhibited the EGFR tyrosine kinase with IC50 values between 1 and 5 nM. In EGF-dependent cellular systems, tyrosine phosphorylation, as well as c-fos mRNA expression, was inhibited with similar IC50 values. Further successful application of this pharmacophore model led to the identification and optimization of phenylamino-pyrazolo[4,3-d]pyrimidines and substituted isoflavones and quinolones, other classes of potent, selective, and ATP competitive EGFR kinase inhibitors with IC50 values in the low nanomolar range. Structure-activity relationships of both classes are discussed.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 48 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:383567 CAPLUS Full-text
DOCUMENT NUMBER: 131:157969
TITLE: N-myristoylation of a peptide substrate for Src converts it into an apparent slow-binding bisubstrate-type inhibitor
AUTHOR(S): Ramdas, L.; Obeyesekere, N. U.; Sun, G.; McMurray, J. S.; Budde, R. J. A.
CORPORATE SOURCE: Department of Neuro-Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Journal of Peptide Research (1999), 53(5), 569-577
CODEN: JPERFA; ISSN: 1397-002X
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The conversion of a peptide substrate to a potent inhibitor by chemical modification is a promising approach in the development of inhibitors for protein tyrosine kinases. N-acylation of the synthetic peptide substrate H-Glu-Phe-Leu-Tyr-Gly-Val-Phe-Asp-NH2 (EFLYGVFD) resulted in synergistic inhibition of Src protein kinase activity that was greater than the inhibition by either free peptide and/or free acyl group. Synergistic inhibition was dependent upon the peptide sequence and the length of the acyl chain. The min. length of the fatty acyl chain to synergistically inhibit Src was a lauryl (C11H23CO) group. N-myristoylated EFLYGVFD (myr-EFLYGVFD) inhibited the phosphorylation of poly E4Y by Src with an apparent Ki of 3 μm, whereas EFLYGVFD and myristic acid inhibited with Ki values of 260 and 35 μm, resp. The nonacylated EFLYGVFD was a substrate for Src with Km and Vmax values of 100 μm and 400 nmol/min/mg protein, resp. However, upon myristoylation, the peptide was no longer a substrate for Src. Both the acylated and non-acylated peptides were competitive inhibitors against the substrate poly E4Y. The non-acylated free peptide showed mixed inhibition against ATP while the myristoylated peptide was competitive against ATP. Myristic acid was uncompetitive against poly E4Y and competitive against ATP. Further anal. indicated that the myristoylated peptide acted as a reversible slow-binding inhibitor with two binding sites on Src. The myristoylated 8-mer peptide was reduced in size to a myristoylated 3-mer without losing the affinity or characteristics of a bisubstrate-type inhibitor. The conversion of a classical reversible inhibitor to a reversible slow-binding multisubstrate analog has improved the potency of inhibition by the peptide.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 49 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:368529 CAPLUS Full-text
DOCUMENT NUMBER: 131:153426
TITLE: Discovery and initial characterization of the paullones, a novel class of small-molecule inhibitors of cyclin-dependent kinases
AUTHOR(S): Zaharevitz, Daniel W.; Gussio, Rick; Leost, Maryse; Senderowicz, Adrian M.; Lahusen, Tyler; Kunick, Conrad; Meijer, Laurent; Sausville, Edward A.
CORPORATE SOURCE: Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD, 20892-7444, USA
SOURCE: Cancer Research (1999), 59(11), 2566-2569
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: AACR Subscription Office
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Anal. of the National Cancer Institute Human Tumor Cell Line Anti-Cancer Drug Screen data using the COMPARE algorithm to detect similarities in the pattern of compound action to flavopiridol, a known inhibitor of cyclin-dependent kinases (CDKs), has suggested several possible novel CDK inhibitors. 9-Bromo-7,12-dihydro-indolo[3,2- d][1]benzazepin-6(5H)-one, NSC-664704 (kenpaullone), is reported here to be a potent inhibitor of CDK1/cyclin B (IC50, 0.4 μM). This compound also inhibited CDK2/cyclin A (IC50, 0.68 μM), CDK2/cyclin E (IC50, 7.5 μM), and CDK5/p25 (IC50, 0.85 μM) but had much less effect on other kinases; only c-src (IC50, 15 μM), casein kinase 2 (IC50, 20 μM), erk 1 (IC50, 20 μM), and erk 2 (IC50, 9 μM) were inhibited with IC50s less than 35 μM. Kenpaullone acts by competitive inhibition of ATP binding. Mol. modeling indicates that kenpaullone can bind in the ATP binding site of CDK2 with residue contacts similar to those observed in the crystal structures of other CDK2-bound inhibitors. Analogs of kenpaullone, in particular 10-bromopaullone (NSC-672234), also inhibited various protein kinases including CDKs. Cells exposed to kenpaullone and 10-bromopaullone display delayed cell cycle progression. Kenpaullone represents a novel chemotype for compds. that preferentially inhibit CDKs.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 50 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:366062 CAPLUS Full-text
DOCUMENT NUMBER: 131:164975
TITLE: Structure-Activity Relationships for 5-Substituted 1-Phenylbenzimidazoles as Selective Inhibitors of the Platelet-Derived Growth Factor Receptor
AUTHOR(S): Palmer, Brian D.; Kraker, Alan J.; Hartl, Brian G.; Panopoulos, Athanasia D.; Panek, Robert L.; Batley, Brian L.; Lu, Gina H.; Trumpp-Kallmeyer, Susanne; Showalter, H. D. Hollis; Denny, William A.
CORPORATE SOURCE: Auckland Cancer Society Research Centre Faculty of Medicine and Health Sciences, The University of Auckland School of Medicine, Auckland, N. Z.
SOURCE: Journal of Medicinal Chemistry (1999), 42(13), 2373-2382
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 131:164975

AB Following an earlier discovery of 1-phenylbenzimidazoles as ATP -site inhibitors of the platelet-derived growth factor receptor (PDGFR), further structure-activity relationships for analogs (particularly 5-substituted derivs.) are reported. The data are consistent with a binding model (constructed from the homol.-modeled structure of the catalytic subunit of the PDGFR using protein kinase A as the template) in which the ligand binds in the relatively narrow ATP site, with the Ph ring pointing toward the interior of the pocket and the 5-position of the benzimidazole ring toward the mouth of the pocket. The narrow binding pocket allows a maximum torsion angle between the Ph and benzimidazole rings of about 40°, consistent with that calculated (43.6°) for the min.-energy conformation of the unsubstituted free ligand. The inactivity of 7- or 2'-substituted analogs is consistent with the greater torsion angle (and thus larger ligand cross-section) of such substituted analogs. There is substantial bulk tolerance for 5-substituents, which protrude out of the mouth of the hydrophobic pocket, with the most effective analogs being those bearing weak bases. On the basis of this model, 5-OR derivs. bearing cationic side chains were prepared as soluble analogs, and these showed sub-micromolar potencies against the isolated PDGFR enzyme. They were also moderately effective inhibitors of autophosphorylation of PDGFR in rat aortic vascular smooth muscle cells, with IC50s in the range 0.1-1 μM.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 51 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:266610 CAPLUS Full-text
DOCUMENT NUMBER: 131:97010
TITLE: Michellamine Alkaloids Inhibit Protein Kinase C
AUTHOR(S): White, E. Lucile; Chao, Wan-ru; Ross, Larry J.; Borhani, David W.; Hobbs, Peter D.; Upender, Velaparthi; Dawson, Marcia I.
CORPORATE SOURCE: Department of Biochemistry, Southern Research Institute, Birmingham, AL, 35205, USA
SOURCE: Archives of Biochemistry and Biophysics (1999), 365(1), 25-30
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Michellamines A, B, and C have shown antiviral activity against HIV-1 and HIV-2 in cell culture. They act in a complex manner by at least two reported antiviral mechanisms, inhibition of HIV reverse transcriptase and inhibition of HIV-induced cellular fusion. On the basis of their structural similarity to other protein kinase C (PKC) inhibitors, we have investigated another possible mechanism-inhibition of PKC. The michellamines were found to inhibit rat brain PKC with IC50 values in the 15-35 μM range. Michellamine B was a noncompetitive PKC inhibitor with respect to ATP with a Ki value of 4-6 μM, whereas mixed-type inhibition was observed when the peptide concentration was varied. Michellamine B inhibited the kinase domain of PKC similarly. These results indicate that the michellamines bind to the PKC kinase domain and not its regulatory domain. Mol. modeling showed that all three michellamines can bind in the active site cleft of the PKC kinase domain, to block both the ATP and the peptide substrate subsites. (c) 1999 Academic Press.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 52 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:242947 CAPLUS Full-text
DOCUMENT NUMBER: 131:55746
TITLE: Dissection of the Nucleotide and Metal-Phosphate Binding Sites in cAMP-Dependent Protein Kinase
AUTHOR(S): Herberg, Friedrich W.; Doyle, Michael L.; Cox, Sarah; Taylor, Susan S.
CORPORATE SOURCE: Institut fuer Physiologische Chemie Abt. fuer Biochemie Supramolekularer Systeme, Ruhr-Universitaet Bochum, Bochum, 44801, Germany
SOURCE: Biochemistry (1999), 38(19), 6352-6360
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The catalytic (C) subunit of cAMP-dependent protein kinase (cAPK) is more stable by several criteria when it is part of a holoenzyme complex. By measuring the thermal stability of the free C subunit in the presence and absence of nucleotides and/or divalent metal ions, it was found that most of the stabilizing effects associated with the type I holoenzyme could be attributed to the nucleotide. The specific requirements for this enhanced stability were further dissected: Adenosine stabilized the C subunit up to 5 °C; however, divalent cations (i.e., Mg2+, Ca2+, and Mn2+) do not increase heat stability in combination with adenosine and adenine (1). Divalent

cations as well as ATP and ADP have no effect by themselves (2). The enhanced stability derived from both ATP and ADP requires divalent cations. MnATP (12 °C) shows a much stronger effect than CaATP (7 °C) and MgATP (5 °C) (3). In the holoenzyme complex or the protein kinase inhibitor/C subunit complex, metal/ATP is also required for enhanced stability; neither the RI or RII subunits nor PKI alone stabilize the C subunit significantly (4). For high thermal stability, the occupation of the second, low-affinity metal-binding site is necessary (5). From these results, we concluded that the adenine moiety works independently from the metal-binding sites, stabilizing the free C subunit by itself. When the β- and γ-phosphates are present, divalent metals are required for positioning these phosphates, and two metals are required to achieve thermostability comparable to adenosine alone. The complex containing two metals is the most stable. A comparison of several conformations of the C subunit derived from different crystal structures is given attributing open and closed forms of the C subunit to less and more thermostable enzymes, resp.

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 53 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:140034 CAPLUS Full-text
DOCUMENT NUMBER: 130:172866
TITLE: Emodin, an anthraquinone derivative isolated from the rhizomes of Rheum palmatum, selectively inhibits the activity of casein kinase II as a competitive inhibitor
AUTHOR(S): Yim, Hyungshin; Lee, Yong Hee; Lee, Chul Hoon; Lee, Seung Ki
CORPORATE SOURCE: College Pharmacy, Seoul National University, Seoul, 151742, S. Korea
SOURCE: Planta Medica (1999), 65(1), 9-13
CODEN: PLMEAA; ISSN: 0032-0943
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Ser/Thr protein kinases play important roles in signal transduction pathways that control the proliferation and differentiation of eukaryotic cells. In this paper, evidence is presented that emodin, an anthraquinone derivative, selectively inhibits casein kinase II (CKII), a Ser/Thr kinase, as a competitive inhibitor. The results with Et acetate exts. of the rhizomes of Rheum palmatum showed that emodin inhibited the activity of cyclin B/cdc2 protein kinase (cdc2). IC50 values for emodin were measured on the activities of several Ser/Thr protein kinases including cAMP-dependent protein kinase (PKA), protein kinase C (PKC), cdc2, casein kinases I (CKI), and CKII. Interestingly, emodin inhibited CKII activity with an IC50 value of 2 μM, which was 2-3 orders of magnitude lower than those against the other kinases. Enzyme kinetic assays showed that emodin inhibited CKII activity as a competitive inhibitor against ATP with a Ki value of 7.2 μM. Collectively, it was suggested that emodin is a selective CKII inhibitor, whose action mechanism is mediated through competitively binding to the ATP binding site.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 54 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:129333 CAPLUS Full-text
DOCUMENT NUMBER: 130:332267
TITLE: Use of a Pharmacophore Model for the Design of EGFR Tyrosine Kinase Inhibitors: Isoflavones and 3-Phenyl-4(1H)-quinolones
AUTHOR(S): Traxler, Peter; Green, Jennifer; Mett, Helmut; Sequin, Urs; Furet, Pascal
CORPORATE SOURCE: NOVARTIS Pharmaceuticals Therapeutic Area Oncology, NOVARTIS Limited, Basel, CH-4002, Switz.
SOURCE: Journal of Medicinal Chemistry (1999), 42(6), 1018-1026
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Using a pharmacophore model for ATP-competitive inhibitors interacting with the active site of the EGFR protein tyrosine kinase together with published X-ray crystal data of quercetin in complex with the Hck tyrosine kinase and of deschloroflavopiridol in complex with CDK2, a putative binding mode of the isoflavone genistein (I) was proposed. Then, based on literature data suggesting that a salicylic acid function, which is represented by the 5-hydroxy-4-keto motif in I, could serve as a pharmacophore replacement of a pyrimidine ring, superposition of I onto the potent EGFR tyrosine kinase inhibitor 4-(3'-chlorophenylamino)-6,7- dimethoxyquinazoline led to 3'-chloro-5,7-dihydroxyisoflavone (II) as a target structure which in fact was 10 times more potent than I. The putative binding mode of II suggests a sulfur-aromatic interaction of the m-chlorophenyl moiety with Cys 773 in the "sugar pocket" of the EGFR kinase model. Replacement of the oxygen in the chromenone ring of II by a nitrogen atom further improved the inhibitory activity against the EGFR kinase.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 55 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:73863 CAPLUS Full-text
DOCUMENT NUMBER: 130:276074
TITLE: Protein kinase inhibitors: structural determinants for target specificity
AUTHOR(S): McMahon, Gerald; Sun, Li; Liang, Congxin; Tang, Cho
CORPORATE SOURCE: SUGEN Inc, Redwood City, CA, 94063, USA
SOURCE: Current Opinion in Drug Discovery & Development (1998), 1(2), 131-146
CODEN: CODDFF; ISSN: 1367-6733
PUBLISHER: Current Drugs Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 142 refs. Advances in ATP site-directed synthetic protein kinase inhibitors, such as quinazolines, 3-arylidenyl indolin-2-ones, pyrido[d]- and pyrimido[d]-pyrimidines, pyrazolo[d]- and pyrrolo[d]-pyrimidines, phenylaminopyrimidines, etc., and x-ray co-crystallog. structures of protein kinases and synthetic inhibitors are discussed.
REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 56 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:73200 CAPLUS Full-text
DOCUMENT NUMBER: 130:278452
TITLE: Determinants of Ligand Binding to cAMP-Dependent Protein Kinase
AUTHOR(S): Huenenberger, Philippe H.; Helms, Volkhard; Narayana, Narendra; Taylor, Susan S.; McCammon, J. Andrew
CORPORATE SOURCE: Department of Chemistry and Biochemistry and Department of Pharmacology, University of California at San Diego, La Jolla, CA, 92093-0365, USA
SOURCE: Biochemistry (1999), 38(8), 2358-2366
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Protein kinases are essential for the regulation of cellular growth and metabolism Since their dysfunction leads to debilitating diseases, they represent key targets for pharmaceutical research. The rational design of kinase inhibitors requires an understanding of the determinants of ligand binding to these proteins. In the present study, a theor. model based on continuum electrostatics and a surface-area-dependent nonpolar term is used to calculate binding affinities of balanol derivs., H-series inhibitors, and ATP analogs toward the catalytic subunit of cAMP-dependent protein kinase (cAPK or protein kinase A). The calcns. reproduce most of the exptl. trends and provide insight into the driving forces responsible for binding. Nonpolar interactions are found to govern protein-ligand affinity. Hydrogen bonds represent a negligible contribution, because hydrogen bond formation in the complex requires the desolvation of the interacting partners. However, the binding affinity is decreased if hydrogen-bonding groups of the ligand remain unsatisfied in the complex. The disposition of hydrogen-bonding groups in the ligand is therefore crucial for binding specificity. These observations should be valuable guides in the design of potent and specific kinase inhibitors.
REFERENCE COUNT: 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 57 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:793407 CAPLUS Full-text
DOCUMENT NUMBER: 130:164704
TITLE: Bivalent Inhibitors of Protein Tyrosine Kinases
AUTHOR(S): Profit, Adam A.; Lee, Tae Ryong; Lawrence, David S.
CORPORATE SOURCE: Department of Biochemistry The Albert Einstein College of Medicine, Yeshiva University, Bronx, NY, 10461, USA
SOURCE: Journal of the American Chemical Society (1999), 121(2), 280-283
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The majority of protein kinase inhibitors described to date are ATP analogs. However, the selectivity of these species is highly suspect, given the enormous number of ATP-dependent processes that transpire in living cells. Inhibitors that target the protein binding site do not suffer from this disadvantage but exhibit comparatively low inhibitory activity. An alternative approach for the design of protein tyrosine kinase inhibitors is described herein. We have constructed species that simultaneously bind to the active site and the SH2 domain of the Src

kinase. Since the region of the inhibitor that assocs. with the SH2 domain coordinates with relatively high affinity, the overall effect is a substantial enhancement in inhibitory potency (230-fold). This design element offers a strategy to overcome the otherwise poor efficacy of peptide-based protein tyrosine kinase inhibitors.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 58 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:724585 CAPLUS Full-text
DOCUMENT NUMBER: 130:90084
TITLE: Crystal structure of an angiogenesis inhibitor bound to the FGF receptor tyrosine kinase domain
AUTHOR(S): Mohammadi, Moosa; Froum, Scott; Hamby, James M.; Schroeder, Mel C.; Panek, Robert L.; Lu, Gina H.; Eliseenkova, Anna V.; Green, David; Schlessinger, Joseph; Hubbard, Stevan R.
CORPORATE SOURCE: Departments of Pharmacology and Medicine, Kaplan Comprehensive Cancer Center, and Skirball Institute of Biomolecular Medicine, New York University Medical Center, New York, NY, 10016, USA
SOURCE: EMBO Journal (1998), 17(20), 5896-5904
CODEN: EMJODG; ISSN: 0261-4189
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Angiogenesis, the sprouting of new blood vessels from pre-existing ones, is an essential physiol. process in development, yet also plays a major role in the progression of human diseases such as diabetic retinopathy, atherosclerosis and cancer. The effects of the most potent angiogenic factors, vascular endothelial growth factor (VEGF), angiopoietin and fibroblast growth factor (FGF) are mediated through cell surface receptors that possess intrinsic protein tyrosine kinase activity. In this report, the authors describe a synthetic compound of the pyrido[2,3-d]pyrimidine class, designated PD 173074, that selectively inhibits the tyrosine kinase activities of the FGF and VEGF receptors. The authors show that systemic administration of PD 173074 in mice can effectively block angiogenesis induced by either FGF or VEGF with no apparent toxicity. To elucidate the determinants of selectivity, the authors have determined the crystal structure of PD 173074 in complex with the tyrosine kinase domain of FGF receptor 1 at 2.5 Å resolution A high degree of surface complementarity between PD 173074 and the hydrophobic, ATP-binding pocket of FGF receptor 1 underlies the potency and selectivity of this inhibitor. PD 173074 is thus a promising candidate for a therapeutic angiogenesis inhibitor to be used in the treatment of cancer and other diseases whose progression is dependent upon new blood vessel formation.

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 59 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:505889 CAPLUS Full-text
Correction of: 1996:73866
DOCUMENT NUMBER: 129:109067
Correction of: 124:232395
TITLE: Tyrosine kinase inhibitors. 9. Synthesis and evaluation of fused tricyclic quinazoline analogs as ATP site inhibitors of the tyrosine kinase activity of the epidermal growth factor receptor
AUTHOR(S): Rewcastle, Gordon W.; Palmer, Brian D.; Bridges, Alexander J.; Showalter, H. D. Hollis; Sun, Li; Nelson, James; McMichael, Amy; Kraker, Alan J.; Fry, David W.; Denny, William A.
CORPORATE SOURCE: School of Medicine, University of Auckland, Auckland, 92019, N. Z.
SOURCE: Journal of Medicinal Chemistry (1996), 39(4), 918-928
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Following the discovery of 4-[(3-bromophenyl)amino]-6,7- dimethoxyquinazoline (PD 153035) as an extremely potent (IC50 0.025 nM) inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR), several fused tricyclic quinazoline analogs have been prepared and evaluated for their ability to inhibit the enzyme. The most potent compound was a linear imidazo[4,5-g]quinazoline, which exhibited an IC50 of 0.008 nM for inhibition of phosphorylation of a fragment of phospholipase C-γ1 as substrate. While N-Me analogs of linear imidazo[4,5-g]quinazolines showed similar potency, analogous N-[2-(dimethylamino)ethyl] derivs. were less effective. The next most potent compds. were linear pyrazoloquinazoline analogs (IC50 0.34 and 0.44 nM) and a pyrroloquinazoline analog (IC50 0.44 nM), while several other linear tricyclic ring systems of similar geometry to linear imidazo[4,5-g]quinazolines (triazolo-, thiazolo-, and

pyrazinoquinazolines) were less effective. In the imidazo[4,5- g]quinazoline and pyrroloquinazoline series, the corresponding angular isomers were also much less effective than the linear ones. These results are consistent with structure-activity relationship studies previously developed for the 4-[(3-bromophenyl)amino]quinazolines, which suggested that small electron-donating substituents at the 6- and 7-positions were desirable for high potency. Cellular studies of a linear imidazo[4,5-g]quinazoline, i.e., N-(3-bromophenyl)-1H-imidazo[4,5-g]quinazolin-8-amine, show that it can enter cells and rapidly and very selectively shut down EGF-stimulated signal transmission by binding competitively at the ATP site of the EGFR. Following the discovery of 4-[(3-bromophenyl)amino]-6,7- dimethoxyquinazoline (PD 153035) as an extremely potent (IC50 0.025 nM) inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR), several fused tricyclic quinazoline analogs have been prepared and evaluated for their ability to inhibit the enzyme. The most potent compound was a linear imidazo[4,5-g]quinazoline, which exhibited an IC50 of 0.008 nM for inhibition of phosphorylation of a fragment of phospholipase C-γ1 as substrate. While N-Me analogs of linear imidazo[4,5-g]quinazolines showed similar potency, analogous N-[2-(dimethylamino)ethyl] derivs. were less effective. The next most potent compds. were linear pyrazoloquinazoline analogs (IC50s 0.34 and 0.44 nM) and a pyrroloquinazoline analog (IC50 0.44 nM), while several other linear tricyclic ring systems of similar geometry to linear imidazo[4,5-g]quinazolines (triazolo-, thiazolo-, and pyrazinoquinazolines) were less effective. In the imidazo[4,5- g]quinazoline and pyrroloquinazoline series, the corresponding angular isomers were also much less effective than the linear ones. These results are consistent with structure-activity relationship studies previously developed for the 4-[(3-bromophenyl)amino]quinazolines, which suggested that small electron-donating substituents at the 6- and 7-positions were desirable for high potency. Cellular studies of a linear imidazo[4,5-g]quinazoline, i.e., N-(3-bromophenyl)-1H-imidazo[4,5-g]quinazolin-8-amine, show that it can enter cells and rapidly and very selectively shut down EGF-stimulated signal transmission by binding competitively at the ATP site of the EGFR.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 60 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:496546 CAPLUS Full-text

DOCUMENT NUMBER: 129:211390

TITLE: 2-Substituted Aminopyrido[2,3-d]pyrimidin-7(8H)-ones. Structure-Activity Relationships Against Selected Tyrosine Kinases and in Vitro and in Vivo Anticancer Activity

AUTHOR(S): Klutchko, Sylvester R.; Hamby, James M.; Boschelli, Diane H.; Wu, Zhipei; Kraker, Alan J.; Amar, Aneesa M.; Hartl, Brian G.; Shen, Cynthia; Klohs, Wayne D.; Steinkampf, Randall W.; Driscoll, Denise L.; Nelson, James M.; Elliott, William L.; Roberts, Billy J.; Stoner, Chad L.; Vincent, Patrick W.; Dykes, Donald J.; Panek, Robert L.; Lu, Gina H.; Major, Terry C.; Dahring, Tawny K.; Hallak, Hussein; Bradford, Laura A.; Showalter, H. D. Hollis; Doherty, Annette M.

CORPORATE SOURCE: Departments of Chemistry Cancer Research Vascular and Cardiac Diseases and Pharmacokinetics and Drug Metabolism Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, MI, 48105, USA

SOURCE: Journal of Medicinal Chemistry (1998), 41(17), 3276-3292
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB While engaged in therapeutic intervention against a number of proliferative diseases, we have discovered the 2-aminopyrido[2,3-d]pyrimidin-7(8H)-ones as a novel class of potent, broadly active tyrosine kinase (TK) inhibitors. An efficient route was developed that enabled the synthesis of a wide variety of analogs with substitution on several positions of the template. Compds. of this series were competitive with ATP and displayed submicromolar to low nanomolar potency against a panel of TKs, including receptor (platelet-derived growth factor, PDGFr; fibroblast growth factor, FGFr; epidermal growth factor, EGFr) and nonreceptor (c-Src) classes. One of the more thoroughly evaluated members was 63 with IC50 values of 0.079 μM (PDGFr), 0.043 μM (bFGFr), 0.044 μM (EGFr), and 0.009 μM (c-Src). In cellular studies, 63 inhibited PDGF-mediated receptor autophosphorylation in a number of cell lines at IC50 values of 0.026-0.002 μM and proliferation of two PDGF-dependent lines at 0.3 μM. It also caused inhibition of soft agar colony formation in three cell lines that overexpress the c-Src TK, with IC50 values of 0.33-1.8 μM. In in vivo studies against a panel of seven xenograft tumor models with known and/or inferred dependence on the EGFr, PDGFr, and c-Src TKs, compound 63 produced a tumor growth delay of 10.6 days against the relatively refractory SK-OV-3 ovarian xenograft and also displayed activity against the HT-29 tumor. In rat oral bioavailability studies, compound 63 plasma concns. declined in a biexponential manner, and systemic plasma clearance was high relative to liver blood flow.

Finally, in rat metabolism studies, HPLC chromatog. identified two metabolites of 63. Because of the excellent potency of 63 against selected TKs, in vitro and in vivo studies are underway for this compound in addnl. tumor models dependent upon PDGFr, FGFr, and c-Src to assess its potential for advancement to clin. trials.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 61 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:494641 CAPLUS Full-text
DOCUMENT NUMBER: 129:227384
TITLE: Exploiting chemical libraries, structure, and genomics in the search for kinase inhibitors
AUTHOR(S): Gray, Nathanael S.; Wodicka, Lisa; Thunnissen, Andy-Mark W. H.; Norman, Thea C.; Kwon, Soojin; Espinoza, F. Hernan; Morgan, David O.; Barnes, Georjana; LeClerc, Sophie; Meijer, Laurent; Kim, Sung-Hou; Lockhart, David J.; Schultz, Peter G.
CORPORATE SOURCE: Howard Hughes Med. Inst., Univ. California, Berkeley, CA, 94720, USA
SOURCE: Science (Washington, D. C.) (1998), 281(5376), 533-538
CODEN: SCIEAS; ISSN: 0036-8075
PUBLISHER: American Association for the Advancement of Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Selective protein kinase inhibitors were developed on the basis of the unexpected binding mode of 2,6,9-trisubstituted purines to the ATP-binding site of the human cyclin-dependent kinase 2 (CDK2). By iterating chemical library synthesis and biol. screening, potent inhibitors of the human CDK2-cyclin A kinase complex and of Saccharomyces cerevisiae Cdc28p were identified. The structural basis for the binding affinity and selectivity was determined by anal. of a three-dimensional crystal structure of a CDK2- inhibitor complex. The cellular effects of these compds. were characterized in mammalian cells and yeast. In the latter case the effects were characterized on a genome-wide scale by monitoring changes in mRNA levels in treated cells with high-d. oligonucleotide probe arrays. Purine libraries could provide useful tools for analyzing a variety of signaling and regulatory pathways and may led to the development of new therapeutics.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 62 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:463340 CAPLUS Full-text
DOCUMENT NUMBER: 129:199739
TITLE: Cyclic peptides as probes of the substrate binding site of the cytosolic tyrosine kinase, pp60c-src1
AUTHOR(S): McMurray, John S.; Budde, Raymond J. A.; Ke, She; Obeyesekere, Nihal U.; Wang, Wei; Ramdas, Latha; Lewis, Claire A.
CORPORATE SOURCE: Department of Neuro-Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Archives of Biochemistry and Biophysics (1998), 355(1), 124-130
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of 48 cyclic peptides based on the amino acid sequence surrounding the autophosphorylation site of pp60c-src was synthesized and each was tested as both a substrate and an inhibitor of this protein tyrosine kinase. Starting with cyclo(Asp1-Asn2-Gln3- Tyr4-Ala5-Ala6-Arg7-Gln8-D-Phe9-Pro10) a six-amino-acid survey was performed at positions 1 through 8 to determine which positions were critical for affinity and phosphorylation and which amino acids produced the greatest activity. Our survey found that Arg7 was detrimental for binding and phosphorylation and that aromatic residues were preferred at this position. Further increases in affinity were obtained with hydrophobic residues at position 6 with the optimum for both affinity and phosphorylation being Phe. Changes on the amino-terminal side of Tyr4 resulted in reduced Vmax values, illustrating the requirement for acidic residues in peptidic tyrosine kinase substrates. The result of the survey was cyclo(Asp1-Asn2-Gln3-Tyr4-Ala5-Phe6-Phe7-Gln8-D-Phe9-Pro10). The change of residues 6 and 7 resulted in a 42-fold increase in affinity and no increase in Vmax. As a substrate, this peptide displayed Michaelis-Menten kinetics at saturating ATP conditions. As an inhibitor, mixed inhibition was observed A linear version of this peptide was 13-fold less potent an inhibitor than the cyclic peptide. (c) 1998 Academic Press.
REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 63 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:429042 CAPLUS Full-text
DOCUMENT NUMBER: 129:117426

TITLE: Synthesis and Biological Evaluations of 3-Substituted Indolin-2-ones: A Novel Class of Tyrosine Kinase Inhibitors That Exhibit Selectivity toward Particular Receptor Tyrosine Kinases
AUTHOR(S): Sun, Li; Tran, Ngoc; Tang, Flora; App, Harald; Hirth, Peter; McMahon, Gerald; Tang, Cho
CORPORATE SOURCE: SUGEN Inc, Redwood City, CA, 94063, USA
SOURCE: Journal of Medicinal Chemistry (1998), 41(14), 2588-2603
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 3-Substituted indolin-2-ones have been designed and synthesized as a novel class of tyrosine kinase inhibitors which exhibit selectivity toward different receptor tyrosine kinases (RTKs). These compds. have been evaluated for their relative inhibitory properties against a panel of RTKs in intact cells. By modifying the 3-substituted indolin-2-ones, we have identified compds. which showed selective inhibition of the ligand-dependent autophosphorylation of various RTKs at submicromolar levels in cells. Structure-activity anal. for these compds. and their relative potency and selectivity to inhibit particular RTKs has determined that (1) 3-[(five-membered heteroaryl ring)methylidenyl]indolin-2-ones are highly specific against the VEGF (Flk-1) RTK activity, (2) 3-(substituted benzylidenyl)indolin-2-ones containing bulky group(s) in the Ph ring at the C-3 position of indolin-2-ones showed high selectivity toward the EGF and Her-2 RTKs, and (3) the compound containing an extended side chain at the C-3 position of the indolin-2-one exhibited high potency and selectivity when tested against the PDGF and VEGF (Flk-1) RTKs. Recent published crystallog. data for two of these 3-substituted indolin-2-ones provides a rationale to suggest that these compds. may bind in the ATP binding pocket of RTKs. The structure-activity anal. supports the use of subsets of these compds. as specific chemical leads for the development of RTK-specific drugs with broad application for the treatment of human diseases.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 64 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:269543 CAPLUS Full-text
DOCUMENT NUMBER: 128:316912
TITLE: Development of a Binding Model to Protein Tyrosine Kinases for Substituted Pyrido[2,3-d]pyrimidine Inhibitors
AUTHOR(S): Trumpp-Kallmeyer, Susanne; Rubin, J. Ronald; Humblet, Christine; Hamby, James M.; Showalter, H. D. Hollis
CORPORATE SOURCE: Division of Warner-Lambert Company, Parke-Davis Pharmaceutical Research, Ann Arbor, MI, 48105, USA
SOURCE: Journal of Medicinal Chemistry (1998), 41(11), 1752-1763
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new class of highly potent tyrosine kinase inhibitors based on the pyrido[2,3-d]pyrimidine core template was previously reported. To understand the structural basis for the potency and specificity, a model for the binding mode of this class of inhibitors to the tyrosine kinase domains of c-Src, PDGFr, FGFr, and EGFr tyrosine kinases was developed from structural information (principally using the catalytic domain of c-AMP-dependent protein kinase as template) and structure-activity relation (SAR) information. In the resulting docking mode, the pyrido[2,3-d]pyrimidine template shows a H-bonding pattern identical to that of olomucine. The 6-aryl substituent of the heterocycle is located deep in the binding cleft in a pocket not used by ATP, which helps to confer high-affinity binding as well as specificity. The 2-anilino and 2-(dialkylamino)alkylamino substituents as well as the 7-urea substituent of inhibitors within this class are located at the entrance of the binding cleft and make contact with residues in the hinge region between the two kinase lobes. This allows considerable variability and bulk tolerance for N-2 and N-7 substituents. The models presented here are consistent with the SAR seen for the inhibition of a number of isolated enzymes and provide a structural basis to explain their specificity. They were used successfully to design new highly potent protein kinase inhibitors.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 65 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:198803 CAPLUS Full-text
DOCUMENT NUMBER: 128:217352
TITLE: Synthesis and biological activity of tyrosine protein kinase inhibitors
AUTHOR(S): Pan, Shuhua; Guo, Zongru; Liang, Xiaotian
CORPORATE SOURCE: Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College,

Beijing, 100050, Peop. Rep. China
SOURCE: Yaoxue Xuebao (1997), 32(7), 515-523
CODEN: YHHPAL; ISSN: 0513-4870
PUBLISHER: Chinese Academy of Medical Sciences, Institute of Materia Media
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB Four classes of 25 tyrosine protein kinase (TPK) inhibitors were designed and synthesized. Inhibiting effects of synthesized compds. on TPK of HL-60 leukemia cell were tested using 32P- ATP method, and some of them exhibited evident inhibitory activities. Their structure-activity relationship were similar to that of TPK inhibitors reported in literatures. Inhibiting effects of synthesized. compds. on TPK of normal rat spleen cell were also tested using ELISA method, and their SAR were different from that using 32P-ATP method.

L7 ANSWER 66 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:141234 CAPLUS Full-text
TITLE: SU5416: A potent and selective Flk-1/KDR kinase inhibitor that blocks receptor autophosphorylation, endothelial cell mitogenesis, and tumor growth
AUTHOR(S): Tang, Cho; Li, Sun; Tran, Jade; Liang, Chris; Nematalla, Asaad; Fong, Annie; App, Harald; Rice, Audie; Kim, Young; Schreck, Randy; Chen, Jason; Dowd, Brian; Suto, Eric; Vasile, Steve; Shawver, Laura; McMahon, Jerry; Hirth, Peter
CORPORATE SOURCE: SUGEN, Inc., Redwood City, CA, 94063, USA
SOURCE: Book of Abstracts, 215th ACS National Meeting, Dallas, March 29-April 2 (1998), MEDI-205. American Chemical Society: Washington, D. C.
CODEN: 65QTAA
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB SU5416, a novel Flk-1/KDR antagonist which inhibits tumor angiogenesis, is currently under evaluation in Phase I clin. studies. SU5416 is a potent and selective inhibitor of Flk-1 tyrosine autophosphorylation with > 20-100-fold less inhibitory activity compared to ligand-stimulated activation of the PDGF, EGF, insulin, and other kinases. SU5416 was shown to inhibit the Flk-1 receptor kinase with an IC50 = 20 nM. Expts. using isolated Flk-1 kinase indicate that SU5416 acts in part as an ATP competitor with a 40-fold higher binding that ATP in the Flk-1 kinase. Crystallog. anal. of related compds. in the ATP binding pocket of the FGF receptor suggests that SU5416 may act, in part, as a Flk-1-specific ATP mimetic. SU5416 was found to exhibit a potent (IC50 = 70 nM) and selective (>700-fold) anti-proliferative effect on VEGF-driven (KDR) human endothelial cells. The synthesis and structure activity relationship of SU5416 and related compds. will be presented.

L7 ANSWER 67 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:141135 CAPLUS Full-text
TITLE: A new class of highly selective protein kinase -inhibitors: Phenylaminopyrimidines
AUTHOR(S): Zimmermann, J.; Buchdunger, E.; Fabbro, D.; Geiger, Th.; Mett, H.; Meyer, Th.; Muller, M.; Ruetz, St.
CORPORATE SOURCE: Oncology Research, Novartis Ltd., Basel, CH-4002, Switz.
SOURCE: Book of Abstracts, 215th ACS National Meeting, Dallas, March 29-April 2 (1998), MEDI-103. American Chemical Society: Washington, D. C.
CODEN: 65QTAA
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Protein kinases, a large family of at least 200 members, play a crucial role in signal transduction as well as in cellular proliferation, differentiation and various regulatory mechanisms. The inhibition of a growth related kinase may therefore provide a new therapy for diseases such as cancer. It was now found that some compds. belonging to the class of phenylamino-pyrimidines are selective inhibitors of either PKC, PDGF-R kinase, cdc2 or abl-kinase. These compds. interfere with the binding of ATP. The structure-activity relationship of this compound class for the inhibition of cdc2 will be discussed, and the surprisingly high selectivity will be documented. The compds. are antiproliferatively active as demonstrated in the inhibition of various cancer cell lines. They also show in vivo anti-tumor activity against different cancer xenografts in nude mice.

L7 ANSWER 68 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:85301 CAPLUS Full-text
DOCUMENT NUMBER: 128:188286

TITLE: Tyrosine Kinase Inhibitors. 14. Structure-Activity Relationships for Methyl- amino-Substituted Derivatives of 4-[(3-Bromophenyl)amino]-6-(methylamino)- pyrido[3,4-d]pyrimidine (PD 158780), a Potent and Specific Inhibitor of the Tyrosine Kinase Activity of Receptors for the EGF Family of Growth Factors

AUTHOR(S): Rewcastle, Gordon W.; Murray, Donna K.; Elliott, William L.; Fry, David W.; Howard, Curtis T.; Nelson, James M.; Roberts, Billy J.; Vincent, Patrick W.; Showalter, H. D. Hollis; Winters, R. Thomas; Denny, William A.

CORPORATE SOURCE: Cancer Society Research Laboratory Faculty of Medicine and Health Science, University of Auckland, Auckland, 92019, N. Z.

SOURCE: Journal of Medicinal Chemistry (1998), 41(5), 742-751
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

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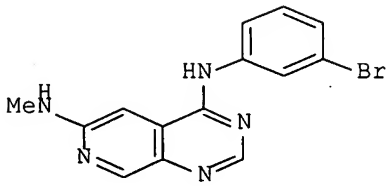

I

AB PD 158780 (I) is a very potent in vitro inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR) (IC50 = 0.08 nM), and other members of the erbB family, by competitive binding at the ATP site of these signal transduction enzymes. A series of analogs of PD 158780 bearing solubilizing functions off the 6-methylamino substituent were prepared by reaction of the 6-fluoro derivs. with appropriate amine nucleophiles. These were evaluated for their ability to inhibit the tyrosine phosphorylating action of EGF-stimulated full-length EGFR enzyme and for inhibition of autophosphorylation of the EGFR in A431 human epidermoid carcinoma cells in culture. The most effective analogs were those bearing weakly basic substituents through a secondary amine linkage, which proved water-soluble (>10 mM) and potent (IC50s generally <1 nM). No clear SAR could be discerned for these compds. with respect to amine base strength or the distance of the cationic center from the chromophore, suggesting that 6-substituents are in a favorable area of bulk tolerance in the enzyme binding site. More distinct SAR emerged for the ability of the compds. to inhibit EGFR autophosphorylation in A431 cells, where analogs bearing lipophilic weak bases were preferred. Representative analogs were evaluated for antitumor effectiveness against four in vivo tumor models. Significant in vivo activity was observed in estrogen-dependent MCF-7 breast and A431 epidermoid tumors. Marginal activity was seen in an EGFR-transfected tumor model, suggesting that while this cell line requires EGF for clone formation in soft agar, other growth factors may be able to replace EGF in vivo. Also, activity was seen against the SK-OV-3 ovarian cancer model, which is known to express other EGF receptor family members (although it is not clear whether these are absolutely required for growth in vivo). While substantial growth delays were seen in A431 and MCF-7 tumor models, the treated tumors remained approx. the same size throughout therapy, suggesting that the compds. are cytostatic rather than cytotoxic under these test conditions. It remains to be determined if more prolonged therapy has cytotoxic effects in vivo, resulting in net tumor cell kill.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 69 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:63589 CAPLUS Full-text

DOCUMENT NUMBER: 128:227773

TITLE: Molecular probes for the binding site of inositol 1,4,5-trisphosphate (IP3) 3-kinase and comparison with IP3 receptor

AUTHOR(S): Choi, Gildon; Chang, Young-Tae; Chung, Sung-Kee; Choi, Kwan Yong

CORPORATE SOURCE: Dep. Life Sciences, Pohang Univ. Sciences Technol., Pohang, 790-784, S. Korea

SOURCE: Korean Journal of Medicinal Chemistry (1997), 7(2),

106-114
CODEN: KJMCE7; ISSN: 1225-0058
PUBLISHER: Korean Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Inositol 1,4,5-triphosphate 3-kinase (IP3K) catalyzes the ATP-dependent phosphorylation of inositol 1,4,5-triphosphate [Ins(1,4,5)P3] generating inositol 1,3,4,5-tetrakisphosphate [Ins(1,3,4,5)P4]. The inhibitory effects of all possible 38 regioisomers of inositol phosphates [InsPn] on the IP3K activity have between examined The correlations between inhibitory potencies and their structural features have allowed an assessment of the environment at the binding site of IP3K and a proposed binding site model, which has been compared with the binding site model of IP3 receptor.
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 70 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:724025 CAPLUS Full-text
DOCUMENT NUMBER: 128:13237
TITLE: Tyrosine Kinase Inhibitors. 13. Structure-Activity Relationships for Soluble 7-Substituted 4-[(3-Bromophenyl)amino]pyrido[4,3-d]pyrimidines Designed as Inhibitors of the Tyrosine Kinase Activity of the Epidermal Growth Factor Receptor
AUTHOR(S): Thompson, Andrew M.; Murray, Donna K.; Elliott, William L.; Fry, David W.; Nelson, James A.; Showalter, H. D. Hollis; Roberts, Bill J.; Vincent, Patrick W.; Denny, William A.
CORPORATE SOURCE: Faculty of Medicine and Health Science, University of Auckland, Auckland, N. Z.
SOURCE: Journal of Medicinal Chemistry (1997), 40(24), 3915-3925
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The general class of 4-(phenylamino)quinazolines are potent (some members with IC50 values «1 nM) and selective inhibitors of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR), via competitive binding at the ATP site of the enzyme, but many of the early analogs had poor aqueous solubility («1 mM). A series of 7-substituted 4-[(3-bromophenyl)amino]pyrido[4,3-d]pyrimidines, together with selected (3-methylphenyl)amino analogs, were prepared by reaction of the analogous 7-fluoro derivs. with appropriate amine nucleophiles in 2-BuOH or aqueous 1-PrOH. All of the compds. were evaluated for their ability to inhibit the tyrosine-phosphorylating action of EGF-stimulated full-length EGFR enzyme. Selected analogs were also evaluated for their inhibition of autophosphorylation of the EGF receptor in A431 human epidermoid carcinoma cells in culture and against A431 tumor xenografts in mice. Analogs bearing a wide variety of polyol, cationic, and anionic solubilizing substituents retained activity, but the most effective in terms of both increased aqueous solubility (>40 mM) and retention of overall inhibitory activity (IC50's of 0.5-10 nM against isolated enzyme and 8-40 nM for inhibition of EGFR autophosphorylation in A431 cells) were weakly basic amine derivs. These results are broadly consistent with a proposed model for the binding of these compds. to EGFR, in which the 6- and 7-positions of the pyridopyrimidine ring are in a largely hydrophobic binding region of considerable steric freedom, at the entrance of the adenine binding cleft. The most active cationic analogs have a weakly basic side chain where the amine moiety is three or more carbon atoms away from the nucleus. Two of the compds. (bearing weakly basic morpholinopropyl and strongly basic (dimethylamino)butyl solubilizing groups) produced in vivo tumor growth delays of 13-21 days against advanced stage A431 epidermoid xenografts in nude mice, when administered i.p. twice per day on days 7-21 posttumor implant. Treated tumors did not increase in size during therapy and resumed growth at the termination of therapy, indicating an apparent cytostatic effect for these compds. under these treatment conditions. The data suggest that continuous long-term therapy with these compds. may result in substantial tumor growth inhibition.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 71 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:638426 CAPLUS Full-text
DOCUMENT NUMBER: 127:272380
TITLE: Use of a Pharmacophore Model for the Design of EGF-R Tyrosine Kinase Inhibitors: 4-(Phenylamino)pyrazolo[3,4-d]pyrimidines
AUTHOR(S): Traxler, Peter; Bold, Guido; Frei, Joerg; Lang, Marc; Lydon, Nicholas; Mett, Helmut; Buchdunger, Elisabeth; Meyer, Thomas; Mueller, Marcel; Furet, Pascal
CORPORATE SOURCE: Novartis Pharmaceuticals Therapeutic Area Oncology

Novartis Limited, Basel, CH-4002, Switz.
SOURCE: Journal of Medicinal Chemistry (1997), 40(22), 3601-3616
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the course of the random screening of a pool of CIBA chems., 2 pyrazolopyrimidines were identified as fairly potent inhibitors of the EGF-R tyrosine kinase. Using a pharmacophore model for ATP-competitive inhibitors interacting with the active site of the EGF-R protein tyrosine kinase (PTK), the class of the pyrazolo[3,4-d]pyrimidines was then optimized in an interactive process leading to a series of 4-(phenylamino)-1H-pyrazolo[3,4- d]pyrimidines as highly potent inhibitors of the EGF-R tyrosine kinase. The most potent compds. of this series inhibited the EGF-R PTK with IC50 values below 10 nM. High selectivity toward a panel of nonreceptor tyrosine kinases (c-SRC, v-Abl) and serine/threonine kinases (PKC α, CDK1) was observed. In cells, EGF-stimulated cellular tyrosine phosphorylation was inhibited by these compds. at IC50 values below 50 nM, whereas PDGF-induced tyrosine phosphorylation was not affected by concns. up to 10 μM, thus indicating high selectivity for the inhibition of the ligand-activated EGF-R signal transduction pathway. Two compds.inhibited proliferation of the EGF-dependent MK cell line with IC50 values below 0.5 μM. In addition, 2 other compds., showing satisfactory oral bioavailability in mice after oral administration, exhibited good in vivo efficacy at doses of 12.5 and 50 mg/kg in a nude mouse tumor model using xenografts of the EGF-R overexpressing A431 cell line. From SAR studies, a binding mode for 4-(phenylamino)-1H-pyrazolo[3,4-d]pyrimidines at the ATP-binding site of the EGF-R tyrosine kinase is proposed. 4-(Phenylamino)-1H-pyrazolo[3,4-d]pyrimidines represent a new class of highly potent tyrosine kinase inhibitors which preferentially inhibit the EGF-mediated signal transduction pathway and have the potential for further evaluation as anticancer agents.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 72 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:589693 CAPLUS Full-text
DOCUMENT NUMBER: 127:272234
TITLE: Inhibition of the HER2 tyrosine kinase and characterization of a hydrophobic site near the nucleotide binding domain
AUTHOR(S): Maddry, Joseph A.; Kussner, Conrad; Truss, Jackie W.; Niwas, Shri; White, E. Lucile; Kwong, Cecil D.
CORPORATE SOURCE: Department of Organic Chemistry, Southern Research Institute, Birmingham, AL, 35255, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1997), 7(16), 2109-2114
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of compds. was prepared to investigate the hydrophobic character of the HER2 receptor tyrosine kinase active site. These bisubstrate analogs contained hydrophobic moieties in place of the polar triphosphate and nucleoside fragments of the natural ATP ligand. Despite these modifications, good affinity was observed as measured by inhibition of receptor autophosphorylation.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 73 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:436125 CAPLUS Full-text
DOCUMENT NUMBER: 127:117061
TITLE: Structure-Activity Relationships for a Novel Series of Pyrido[2,3-d]pyrimidine Tyrosine Kinase Inhibitors
AUTHOR(S): Hamby, James M.; Connolly, Cleo J. C.; Schroeder, Mel C.; Winters, R. Thomas; Showalter, H. D. Hollis; Panek, Robert L.; Major, Terry C.; Olsewski, Bronislawa; Ryan, Michael J.; Dahring, Tawny; Lu, Gina H.; Keiser, Joan; Amar, Aneesa; Shen, Cindy; Kraker, Alan J.; Slintak, Veronika; Nelson, James M.; Fry, David W.; Bradford, Laura; Hallak, Hussein; Doherty, Annette M.
CORPORATE SOURCE: Parke-Davis Pharmaceutical Research, Division of Warner Lambert Company, Ann Arbor, MI, 48105, USA
SOURCE: Journal of Medicinal Chemistry (1997), 40(15), 2296-2303
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Screening of a compound library for inhibitors of the fibroblast growth factor (FGFr) and platelet-derived growth factor (PDGFr) receptor tyrosine kinases led to the development of a novel series of ATP competitive pyrido[2,3-d]pyrimidine tyrosine kinase inhibitors. The initial lead, 1-[2-amino-6-(2,6- dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-3-tert-butylurea (I; PD-089828), was found to be a broadly active tyrosine kinase inhibitor. I inhibited the PDGFr, FGFr, EGFr, and c-src tyrosine kinases with IC50 values of 1.11, 0.13, 0.45, and 0.22 μM, resp. Subsequent SAR studies led to the synthesis of new analogs with improved potency, solubility, and bioavailability relative to the initial lead. For example, the introduction of a [4-(diethylamino)butyl]amino side chain into the 2-position of I afforded a compound (II) with enhanced potency and bioavailability. II inhibited PDGF-stimulated vascular smooth muscle cell proliferation with an IC50 of 0.3 μM. Furthermore, replacement of the 6-(2,6-dichlorophenyl) moiety of I with a 6-(3',5'-dimethoxyphenyl) functionality produced a highly selective FGFr tyrosine kinase inhibitor (III). III inhibited the FGFr tyrosine kinase with an IC50 of 0.060 μM, whereas IC50s for the inhibition of the PDGFr, FGFr, EGFr, c-src, and InsR tyrosine kinases for this compound were all greater than 50 μM.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 74 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1997:424004 CAPLUS Full-text

DOCUMENT NUMBER: 127:145143

TITLE: Effect of protein kinase inhibitors on activity of mammalian small heat-shock protein (HSP25) kinase

AUTHOR(S): Hayess, Katrin; Benndorf, Rainer

CORPORATE SOURCE: MAX-DELBRUCK-CENTER FOR MOLECULAR MEDICINE, Berlin, 13122, Germany

SOURCE: Biochemical Pharmacology (1997), 53(9), 1239-1247
CODEN: BCPCA6; ISSN: 0006-2952

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The aim of this study was to investigate different protein kinase inhibitors (secondary metabolite-derived substances, synthetic compds., and substrate-based peptides) for their potency to inhibit the mammalian small heat shock protein (HSP25) kinase (E.C. 2.7.1.37) isolated from Ehrlich ascites tumor cells. Among the secondary metabolite-derived inhibitors (staurosporine, K-252a, K-252b, KT5926, KT5720, erbstatin analog, and quercetin) and synthetic compds. (H-9, H-89, HA 1004, KN-62, ML-7, tyrphostin A25, and tyrphostin B42), KT5926, staurosporine, and K-252a inhibited HSP25 kinase most efficiently. Kinetic anal. revealed that inhibition by staurosporine (Ki = 32.4 nM) and K-252a (Ki = 13.7 nM) was competitive with ATP. Inhibition by KT5926 was competitive with the substrate peptide KKKALNRQLSVAA (Ki = 27.2 nM) and noncompetitive with respect to ATP (Ki = 38.8 nM). In comparison with other protein kinases, HSP25 kinase was relatively resistant to most of the inhibitors. KT5926 was the only tested inhibitor with certain preference for HSP25 kinase when compared with protein kinases A, C, and G. Among the tested substrate-based peptides, we identified one peptide (KKKALNRQLGVAA), which preferentially inhibited HSP25 kinase in comparison with protein kinases A and C and mitogen-activated protein kinase. This peptide inhibited HSP25 kinase competitively with the substrate peptide (Ki = 8.1 μM) and noncompetitively with ATP (Ki = 134 μM). A peptide (SRVLKEDKERWEDVK) derived from the putative autoinhibitory domain of the closely related human mitogen-activated protein kinase-activated protein kinase-2 did not inhibit HSP25 kinase activity, suggesting the existence of several species of HSP25 kinases. Furthermore, the data identified structural requirements for inhibitors of HSP25- kinase.

L7 ANSWER 75 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1997:320922 CAPLUS Full-text

DOCUMENT NUMBER: 126:324949

TITLE: Tyrosine Kinase Inhibitors. 12. Synthesis and Structure-Activity Relationships for 6-Substituted 4-(Phenylamino)pyrimido[5,4-d]pyrimidines Designed as Inhibitors of the Epidermal Growth Factor Receptor

AUTHOR(S): Rewcastle, Gordon W.; Bridges, Alexander J.; Fry, David W.; Rubin, J. Ronald; Denny, William A.

CORPORATE SOURCE: Cancer Research Laboratory Faculty of Medicine and Health Sciences, University of Auckland School of Medicine, Auckland, N. Z.

SOURCE: Journal of Medicinal Chemistry (1997), 40(12), 1820-1826
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A series of 6-substituted 4-anilinopyrimido[5,4-d]pyrimidines has been prepared and shown to be potent inhibitors of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR). These compds. are structurally related to the pyrido[3,2-d]- and pyrido[3,4-d]pyrimidines previously shown to be EGFR inhibitors. Their structure-activity relationships (SAR) for inhibition of the isolated enzyme more closely resemble those of the [3,2-d] than the [3,4-d] pyridopyrimidine isomers. This suggests the requirement of an aza atom in the 7- but not the 5-position (i.e., a carbon atom in the 5-position) for the enhanced potency shown by 6-N-methylated derivs. in each series. X-ray crystal structures were determined for the three NHMe derivs. in the pyrido[3,2-d]-, pyrido[3,4-d]-, and pyrimido[5,4-d]pyrimidine series, resp. These show that a carbon rather than a nitrogen atom at the 5-position leads to significant conformational changes in the mol. (a longer C5a-C4 bond and a 30° out-of-plane rotation of the Ph group), due to the requirement to relieve nonbonding interactions between the C5 and N9 protons. Pyrimido[5,4-d]pyrimidine analogs bearing bulky, weakly basic solubilizing side chains linked to the 6-position through a secondary amine generally retained potency both against the isolated enzyme and for inhibition of autophosphorylation of EGFR in intact A431 cells. This agrees with a recent binding model that suggests this general class of compds. binds to EGFR with the 6-position located in an area of comparative bulk tolerance at the entrance to the ATP-binding pocket. While these solubilized pyrimido[5,4-d]pyrimidine analogs were less potent than the NHMe derivative in the isolated enzyme assay, some were considerably superior (and among the most potent ever reported) as inhibitors of EGFR autophosphorylation in cellular assays.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 76 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:301035 CAPLUS Full-text
DOCUMENT NUMBER: 127:18
TITLE: Design and synthesis of novel tyrosine kinase inhibitors using a pharmacophore model of the ATP-binding site of the EGF-R
AUTHOR(S): Traxler, Peter; Furet, Pascal; Mett, Helmut; Buchdunger, Elisabeth; Meyer, Thomas; Lydon, Nicholas
CORPORATE SOURCE: CIBA Pharm. Div., Cancer Bone Metabolism Res. Dep., CIBA Ltd., Basel, CH-4002, Switz.
SOURCE: Journal de Pharmacie de Belgique (1997), 52(2), 88-96
CODEN: JPBEAJ; ISSN: 0047-2166
PUBLISHER: Masson
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 29 refs. One of the most promising targets for the rational design of anti-cancer drugs is the family of the EGF-receptor protein tyrosine kinases. Despite the high sequence homol. within the ATP-binding region of protein tyrosine and/or serine threonine kinases, ATP-competitive compds. have the potential to be selective inhibitors of protein kinases. Dianilino-phthalimides CGP 52 411 nd CGP 53 353 have been identified as potent and ATP-competitive inhibitors of the EGF-R tyrosine kinase with no or only minor activity against a panel of tyrosine and serine/threonine kinases. Using a calculated 3-D computer model of the catalytic domain of the EGF-R tyrosine kinase together with CGP 52 411 as example of an ATP -competitive inhibitor, a pharmacophore model for ATP -competitive inhibitors in the active site of the EGF-R PTK was developed. With the help of this model, 4-phenylamino-7H-pyrrolo[2,3- d]pyrimidines were then identified as new potent EGF-R PTK inhibitors. In an interactive process, the class of the 4-phenylamino-pyrrolo-pyrimidines was optimized and structure- activity-relationship of a series of derivs. thereof are discussed. In vitro, the most active compds. (CGP 59 326, CGP 60 261, CGP 62 706) inhibited the EGF-R tyrosine kinase with IC50 value between 6-30 nM. High selectivity towards a panel of non-receptor tyrosine kinases (c-SRC, v-Abl) and serine/threonine kinases (PKC α, PKA) was observed Kinetic anal. revealed competitive type kinetics relative to ATP. In cells, EGF-stimulated cellular tyrosine phosphorylation was inhibited by these compds. at IC50 values between 0.1-0.3 μM, whereas the ligand-induced receptor autophosphorylation of the PDGF-R was not effected by concns. up to 100 μM. Furthermore, CGP 59 326, CGP 60 261, CGP 62 706 were able to selectively inhibit c-fos mRNA expression in EGF-dependent cell lines with (IC50 approx. 0.1-1 μM) but not in EGF-independent cell systems (IC50>100 μM). Proliferation of the EGF-dependent MK cell line was inhibited with similar IC50 values. In addition, CGP 59 326 and CGP 62 706 showed good in vivo efficacy at low doses after oral or s.c. administration in nude mice tumor models using xenografts of the EGF-dependent A431 cell lines. The ED50 values were between 1.5-2 mg/kg. Phenylamino-pyrrolo-pyrimidines therefore represent a new series of tyrosine kinase inhibitors which preferentially inhibit the EGF-mediated signal transduction pathway and have the characteristics for further evaluation as anticancer agents.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 77 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:262273 CAPLUS Full-text
DOCUMENT NUMBER: 126:277441
TITLE: Tyrosine Kinase Inhibitors. 11. Soluble Analogs of Pyrrolo- and Pyrazoloquinazolines

as Epidermal Growth Factor Receptor Inhibitors : Synthesis, Biological Evaluation, and Modeling of the Mode of Binding

AUTHOR(S): Palmer, Brian D.; Trumpp-Kallmeyer, Susanne; Fry, David W.; Nelson, James M.; Showalter, H. D. Hollis; Denny, William A.

CORPORATE SOURCE: Cancer Society Research Laboratory Faculty of Medicine and Health Science, University of Auckland School of Medicine, Auckland, 1000, N. Z.

SOURCE: Journal of Medicinal Chemistry (1997), 40(10), 1519-1529
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A new route to N-1-substituted pyrazolo- and pyrroloquinazolines has been developed from known quinazolones, via conversion to the corresponding thiones, S-methylation to the thioethers, N-1-alkylation, and coupling with 3-bromoaniline. C-3-Substituted pyrroloquinazolines were prepared by Mannich base chemical A series of compds. bearing solubilizing side chains at these positions has been prepared and evaluated for inhibition of the tyrosine kinase activity of the isolated epidermal growth factor receptor (EGFR) and of its autophosphorylation in EGF-stimulated A431 cells. Several analogs, particularly C-3-substituted pyrroloquinazolines, retained high potency in both assays. A model for the binding of the general class of 4-anilinoquinazolines to the EGFR was constructed from structural information (particularly for the catalytic subunit of the cAMP-dependent protein kinase) and structure- activity relationships (SAR) in the series. In this model, the pyrrole ring in pyrroloquinazolines (and the 6- and 7-positions of quinazoline and related pyridopyrimidine inhibitors) occupies the entrance of the ATP binding pocket of the enzyme, with the pyrrole nitrogen located at the bottom of the cleft and the pyrrole C-3 position pointing toward a pocket corresponding to the ribose binding site of ATP. This allows considerable bulk tolerance for C-3 substituents and lesser but still significant bulk tolerance for N-1 substituents. The observed high selectivity of these compds. for binding to EGFR over other similar tyrosine kinases is attributed to the 4-anilino ring binding in an adjacent hydrophobic pocket which has an amino acid composition unique to the EGFR. The SAR seen for inhibition of the isolated enzyme by the pyrazolo- and pyrroloquinazolines discussed here is fully consistent with this binding model. For the N-1-substituted compds., inhibition of autophosphorylation in A431 cells correlates well with inhibition of the isolated enzyme, as seen previously for related pyridopyrimidines. However, the C-3-substituted pyrroloquinazolines show unexpectedly high potencies in the autophosphorylation assay, making them of particular interest.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 78 OF 114 CAPLUS

ACCESSION NUMBER: 1997:127318 CAPLUS Full-text

DOCUMENT NUMBER: 126:144333

TITLE: Tyrosine kinase inhibitors. 6. Structure-activity relationships among N- and 3-substituted 2,2'-diselenobis(1H-indoles) for inhibition of protein tyrosine kinases and comparative in vitro and in vivo studies against selected sulfur congeners

AUTHOR(S): Showalter, H. D. Hollis; Sercel, Anthony D.; Leja, Boguslawa M.; Wolfangel, Craig D.; Ambroso, Linda A.; Elliott, William L.; Fry, David W.; Kraker, Alan J.; Howard, Curtis T.; Lu, Gina H.; Moore, Charles W.; Nelson, Jamers M.; Roberts, Bill J.; Vincent, Patrick W.; Denny, William A.; Thompson, Andrew M.

CORPORATE SOURCE: Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, MI, 8106-1047, USA

SOURCE: Journal of Medicinal Chemistry (1997), 40(4), 413-426
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 126:144333

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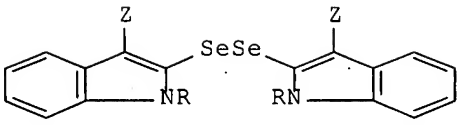


I

AB A small series of 2,2'-diselenobis(1H-indoles), I (e.g. R = Me, H; Z = C(O)NHMe, C(O)NH(CH2)2NEt2) was synthesized as redox-modified congeners of an earlier reported 2,2'-dithiobis(1H-indole) series, starting from 2-halo-3-indolecarboxylic acid precursors bearing various polar functionalities at the C-3 position and small alkyl substituents at the N-1 position of the indole nucleus. Addnl. compds. were derived from (R)- or (S)-tryptophan via a novel application of Se2Cl2 as an electrophilic source of Se2, and a much improved process to a 2,2'-dithiobis(1H-indole) congener was developed using S2Cl2 as a source of S2. Against isolated EGF receptor (EGFr), PDGF receptor (PDGFr), and v-src tyrosine kinases, compds. in this series displayed broad inhibitory activity with IC50 = 0.9->100 μM vs. EGFr, 3.4->50 μM vs. PDGFr, and 0.4-6.7 μM vs. v-src. In general, compds. derived from tryptophan displayed the greatest potency against EGFr and those from 2-halo-3-indolecarboxylic acids greater potency against PDGFr and v-src. Enzyme kinetic studies showed that both classes of compds. display primarily noncompetitive inhibition with respect to either ATP or peptide substrate. DTT caused a general decrease in inhibition of the EGFr and v-src tyrosine kinases by both the diselenium and disulfur series with the reversal of enzyme inhibition occurring less readily within the diselenium series. In whole-cell studies, compds. of this class were growth inhibitory against Swiss 3T3 mouse fibroblasts with IC50 values 0.5-19.5 μM, and the observed structure- activity relationship was different from that of the 2,2'-dithiobis(1H-indoles). A comparative study in the same cell line on the effects of the 2,2'-diselenobis(1H-indole) derived from (R)-tryptophan vs. its disulfur congener on growth factor-mediated tyrosine phosphorylation showed that this compound significantly inhibited EGFr and PDGFr autophosphorylation (in response to its ligand) with complete suppression at 25 and 5 μM, resp. Tyrosine phosphorylation of an 85-kDa protein typically phosphorylated in response to basic FGF was also exquisitely sensitive to this compound, and it displayed inhibitory effects on DNA, RNA, and protein synthesis at submicromolar concns. The disulfur congener exhibited a qual. similar pattern; however, its potency was 10-fold less. This same diselenium/disulfur pair was evaluated in vivo against murine tumors (B16 melanoma, colon carcinoma 26, M5076 sarcoma) and human tumor xenografts (A431 epidermoid tumor, C6 glioma). At maximum tolerated doses (1.8 and 5.0 mg/kg/injection, resp.), neither the diselenium nor disulfur congener was effective against the C6 glioma when administered i.p. daily for 9 days. Studies were also carried out against the A431 epidermoid xenograft to evaluate the same pair of compds. via continuous s.c. infusion from Alzet miniosmotic pumps. The maximum dose that could be administered daily was limited by compound solubility Neither compound produced an antitumor effect in a 7-day continuous infusion study. In the 27-day study, the disulfur compound was inactive whereas the diselenium compound produced a 10.8-day growth delay without appreciable treatment-related weight loss. The in vitro and in vivo findings offer a mechanistic rationale as to why the 2,2'-diselenobis(1H-indoles) are more potent inhibitors than their disulfur congeners.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 79 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:56397 CAPLUS Full-text
DOCUMENT NUMBER: 126:168262
TITLE: Nonphosphorylatable tyrosine surrogates. Implications for protein kinase inhibitor design
AUTHOR(S): Niu, Jinkui; Lawrence, David S.
CORPORATE SOURCE: Dep. Biochemistry, Albert Einstein College Med. Yeshiva Univ., Bronx, NY, 10461, USA
SOURCE: Journal of Biological Chemistry (1997), 272(3), 1493-1499
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tyrosine-specific protein kinases are known to utilize short synthetic tyrosine-containing peptides as substrates and, as a consequence, a number of inhibitory peptides have been prepared by replacing the tyrosine moiety in these peptides with a nonphosphorylatable phenylalanine residue. Unfortunately, the inhibitory efficacy of these phenylalanine-based peptides is often disappointing. These results demonstrate the need for nonphosphorylatable tyrosine surrogates that enhance enzyme affinity. As a consequence, we prepared nearly two dozen different phenethylamine derivs., attached them to the C terminus of an active site-directed peptide (Glu-Glu-Leu-Leu), and examined their effectiveness as inhibitors of pp60c-src. Three derivs. exhibit enhanced inhibitory activity (relative to phenethylamine), including para-substituted sulfonamide

and guanidino analogs as well as a pentafluoro-containing species. The para-sulfonamide derivative was selected for further study and was found to function as a competitive inhibitor vs. variable peptide substrate and as a noncompetitive inhibitor vs. variable ATP. In short, the enhanced inhibitory activity of the sulfonamide derivative is not due to the association of this moiety with the ATP binding site. Furthermore, peptides containing the para-guanidino and pentafluoro derivs. of phenylalanine were prepared These species also display enhanced inhibitory activity toward pp60c-src relative to the corresponding phenylalanine-based peptide.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 80 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:681487 CAPLUS Full-text
DOCUMENT NUMBER: 126:42241
TITLE: Tyrphostins. 6. Dimeric Benzylidenemalononitrile Tyrphostins: Potent Inhibitors of EGF Receptor Tyrosine Kinase in Vitro
AUTHOR(S): Gazit, Aviv; Osherov, Nir; Gilon, Chaim; Levitzki, Alexander
CORPORATE SOURCE: Institute of Chemistry and Life Sciences, Hebrew University of Jerusalem, Jerusalem, 91904, Israel
SOURCE: Journal of Medicinal Chemistry (1996), 39(25), 4905-4911
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Benzylidenemalononitrile (BMN) tyrphostins were previously found to be potent inhibitors of EGF receptor (EGFR) tyrosine kinase activity. Since these compds. were found to compete for the substrate and sometimes with the ATP site and since EGFR acts as a dimer, the authors prepared a series of dimeric tyrphostins. These dimeric tyrphostins were built from 2 BMN units linked by various spacers and designed to fit the dimeric cross-autophosphorylation signal transduction intermediate of the EGFR tyrosine kinases. The structure- activity relationship of these potent dimeric EGF receptor tyrosine kinase inhibitors was reported.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 81 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:536936 CAPLUS Full-text
Correction of: 1996:73866
DOCUMENT NUMBER: 125:195598
Correction of: 124:232395
TITLE: Tyrosine kinase inhibitors. 9. Synthesis and evaluation of fused tricyclic quinazoline analogs as ATP site inhibitors of the tyrosine kinase activity of the epidermal growth factor receptor
AUTHOR(S): Rewcastle, Gordon W.; Palmer, Brian D.; Bridges, Alexander J.; Showalter, H. D. Hollis; Sun, Li; Nelson, James; McMichael, Amy; Kraker, Alan J.; Fry, David W.; Denny, William A.
CORPORATE SOURCE: Sch. Med., Univ. Auckland, Auckland, 92019, N. Z.
SOURCE: Journal of Medicinal Chemistry (1996), 39(4), 918-928
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Following the discovery of 4-[(3-bromophenyl)amino]-6,7- dimethoxyquinazoline (PD 153035) as an extremely potent (IC50 0.025 nM) inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR), several fused tricyclic quinazoline analogs have been prepared and evaluated for their ability to inhibit the enzyme. The most potent compound was a linear imidazo[4,5-g]quinazoline, which exhibited an IC50 of 0.008 nM for inhibition of phosphorylation of a fragment of phospholipase C-γ1 as substrate. While N-Me analogs of linear imidazo[4,5-g]quinazolines showed similar potency, analogous N-[2-(dimethylamino)ethyl] derivs. were less effective. The next most potent compds. were linear pyrazoloquinazoline analogs (IC50 0.34 and 0.44 nM) and a pyrroloquinazoline analog (IC50 0.44 nM), while several other linear tricyclic ring systems of similar geometry to linear imidazo[4,5-g]quinazolines (triazolo-, thiazolo-, and pyrazinoquinazolines) were less effective. In the imidazo[4,5- g]quinazoline and pyrroloquinazoline series, the corresponding angular isomers were also much less effective than the linear ones. These results are consistent with structure-activity relationship studies previously developed for the 4-[(3-bromophenyl)amino]quinazolines, which suggested that small electron-donating substituents at the 6- and 7-positions were desirable for high potency. Cellular studies of a linear imidazo[4,5-g]quinazoline, i.e., N-(3-bromophenyl)-1H-imidazo[4,5-g]quinazolin-8-amine, show that it can enter cells and rapidly and very selectively shut down EGF-stimulated signal transmission by binding competitively at the ATP site of the EGFR.

L7 ANSWER 82 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:495435 CAPLUS Full-text
DOCUMENT NUMBER: 125:184908
TITLE: Phenylamino-pyrimidine (PAP) derivatives: a new class of potent and selective inhibitors of protein kinase C (PKC)
AUTHOR(S): Zimmermann, Juerg; Caravatti, Giorgio; Mett, Helmut; Meyer, Thomas; Mueller, Marcel; Lydon, Nicholas B.; Fabbro, Doriano
CORPORATE SOURCE: CIBA Pharmaceuticals Div., Oncology Virology Res. Dep., Ciba-Geigy Limited, Basel, CH-4002, Switz.
SOURCE: Archiv der Pharmazie (Weinheim, Germany) (1996), 329(7), 371-376
CODEN: ARPMAS; ISSN: 0365-6233
PUBLISHER: VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 125:184908
AB Phenylamino-pyrimidines represent a novel class of inhibitors of protein kinase C with a high degree of selectivity vs. other serine/threonine and tyrosine kinases. Steady state kinetic anal. of N-(3-[1-imidazolyl]-phenyl)-4-(3-pyridyl)-2-pyrimidinamine , which showed potent inhibitory activity, revealed competitive kinetics relative to ATP. The adjacent H-bond acceptor of the pyrimidine moiety next to an H-bond donor of the phenylamine was found to be crucial for inhibitory activity. N-(3-Nitro-phenyl)-4-(3-pyridyl)-2- pyrimidinamine preferentially inhibited PKC-α (IC50 = 0.79 μM) and not the other subtypes tested. The inhibition consts. of PKC-α and the antiproliferative effect on T24 human bladder carcinoma cells showed a qual. correlation, although with some exceptions.

L7 ANSWER 83 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:414641 CAPLUS Full-text
TITLE: Phenylamino-pyrimidines: A new class of potent and selective protein kinase inhibitors
AUTHOR(S): Zimmermann, J.; Buchdunger, E.; Fabbro, D.; Lydon, N.; Mett, H.; Meyer, Th.; Muller, M.
CORPORATE SOURCE: Pharmaceuticals Division, CIBA-GEIGY, Basel, CH-4002, Switz.
SOURCE: Book of Abstracts, 212th ACS National Meeting, Orlando, FL, August 25-29 (1996), MEDI-053. American Chemical Society: Washington, D. C.
CODEN: 63BFAF
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Protein kinases, a large family of at least 200 members, play a crucial role in signal transduction as well as in cellular proliferation, differentiation and various regulatory mechanisms. The inhibition of a growth related kinase may therefore provide a new therapy for diseases such as cancer. It was now found that some compds. belonging to the class of phenylamino-pyrimidines are selective inhibitors of either PKC, PDGF-R kinase, cdc2 or abl-kinase. These compds. interfere with the binding of ATP. The structure-activity relationship of this compound class for the inhibition of these kinases will be discussed, and the surprisingly high selectivity will be documented. The compds. are antiproliferatively active as demonstrated in the inhibition of various cancer cell lines. They also show in vivo anti-tumor activity against different cancer xenografts in nude mice. Particularly, the high selectivity found in vitro for the PDGF-R kinase inhibitor could be translated to the in vivo situation: only the PDGF-driven tumor growth could be stopped whereas an EGF-dependent tumor (A431) was not affected by the compound

L7 ANSWER 84 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:312235 CAPLUS Full-text
DOCUMENT NUMBER: 125:25623
TITLE: Structure-activity relationships for 4-anilinoquinazolines as potent inhibitors at the ATP binding site of the epidermal growth factor receptor in vitro
AUTHOR(S): Denny, William A.; Rewcastle, Gordon W.; Bridges, Alexander J.; Fry, David W.; Kraker, Alan J.
CORPORATE SOURCE: Cancer Research Lab., Univ. Auckland School Medicine, Auckland, 92019, N. Z.
SOURCE: Clinical and Experimental Pharmacology and Physiology (1996), 23(5), 424-427
CODEN: CEXPB9; ISSN: 0305-1870

PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Structure-activity relationships are described for the inhibition of the tyrosine kinase activity (phosphorylation of a fragment of phospholipase Cg1) of the epidermal growth factor receptor (EGFR) by 4-anilinoquinazolines. These compds. are competitive inhibitors at the ATP binding site. The preferred side chain is anilino-, substituted at the 3-position with small lipophilic groups. The quinazoline moiety is absolutely required for activity, but substituents on the quinazoline greatly modulate potency, with electron-donating groups favored. The most potent analog, the 6,7-dimethoxy derivative, has an IC50 of 29 pmol/L and a very high selectivity for the EGFR over other tyrosine kinase enzymes. The present study shows that it is possible to identify small mols. that are very potent, yet highly selective, inhibitors of a single component of the growth signal transduction pathway in cells.

L7 ANSWER 85 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:73866 CAPLUS Full-text
DOCUMENT NUMBER: 124:232395
TITLE: Tyrosine Kinase Inhibitors. 9. Synthesis and Evaluation of Fused Tricyclic Quinazoline Analogs as ATP Site Inhibitors of the Tyrosine Kinase Activity of the Epidermal Growth Factor Receptor
AUTHOR(S): Rewcastle, Gordon W.; Palmer, Brian D.; Bridges, Alexander J.; Showalter, H. D. Hollis; Sun, Li; Nelson, James; McMichael, Amy; Kraker, Alan J.; Fry, David W.; Denny, William A.
CORPORATE SOURCE: School of Medicine, University of Auckland, Auckland, 92019, N. Z.
SOURCE: Journal of Medicinal Chemistry (1996), 39(4), 918-28
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Following the discovery of 4-[(3-bromophenyl)amino]-6,7- dimethoxyquinazoline (PD 153035) as an extremely potent (IC50 0.025 nM) inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR), several fused tricyclic quinazoline analogs have been prepared and evaluated for their ability to inhibit the enzyme. The most potent compound was a linear imidazo[4,5-g]quinazoline, which exhibited an IC50 of 0.008 nM for inhibition of phosphorylation of a fragment of phospholipase C-γ1 as substrate. While N-Me analogs of linear imidazo[4,5-g]quinazolines showed similar potency, analogous N-[2-(dimethylamino)ethyl] derivs. were less effective. The next most potent compds. were linear pyrazoloquinazoline analogs (IC50s 0.34 and 0.44 nM) and a pyrroloquinazoline analog (IC50 0.44 nM), while several other linear tricyclic ring systems of similar geometry to linear imidazo[4,5-g]quinazolines (triazolo-, thiazolo-, and pyrazinoquinazolines) were less effective. In the imidazo[4,5- g]quinazoline and pyrroloquinazoline series, the corresponding angular isomers were also much less effective than the linear ones. These results are consistent with structure-activity relationship studies previously developed for the 4-[(3-bromophenyl)amino]quinazolines, which suggested that small electron-donating substituents at the 6- and 7-positions were desirable for high potency. Cellular studies of a linear imidazo[4,5-g]quinazoline, i.e., N-(3-bromophenyl)-1H-imidazo[4,5-g]quinazolin-8-amine, show that it can enter cells and rapidly and very selectively shut down EGF-stimulated signal transmission by binding competitively at the ATP site of the EGFR.

L7 ANSWER 86 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:51307 CAPLUS Full-text
DOCUMENT NUMBER: 124:164304
TITLE: Modeling study of protein kinase inhibitors: binding mode of staurosporine and origin of the selectivity of CGP 52411
AUTHOR(S): Furet, Pascal; Caravatti, Giorgio; Lydon, Nicholas; Priestle, John P.; Sowadski, Janusz M.; Trinks, Uwe; Traxler, Peter
CORPORATE SOURCE: Pharmaceuticals Division, Ciba-Geigy, Basel, CH-4002, Switz.
SOURCE: Journal of Computer-Aided Molecular Design (1995), 9(6), 465-72
CODEN: JCADEQ; ISSN: 0920-654X
PUBLISHER: ESCOM
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A model for the binding mode of the potent protein kinase inhibitor staurosporine is proposed. Using the information provided by the crystal structure of the cAMP-dependent protein kinase, it is suggested that staurosporine, despite a seemingly unrelated chemical structure, exploits the same key hydrogen-bond interactions as ATP, the cofactor of the protein kinases , in its binding

mode. The structure-activity relationships of the inhibitor and a docking anal. give strong support to this hypothesis. The selectivity of the dianilinophthalimide inhibitor CGP 52411 towards the EGF-receptor protein tyrosine kinase is rationalized on the basis of the model. It is proposed that this selectivity originates in the occupancy, by one of the anilino moieties of the inhibitor, of the region of the enzyme cleft that normally binds the ribose ring of ATP, which appears to possess a marked lipophilic character in this kinase.

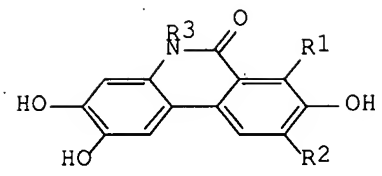
L7 ANSWER 87 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1995:983167 CAPLUS Full-text
DOCUMENT NUMBER: 124:21051
TITLE: Tyrosine kinase inhibitors: unusually steep structure-activity relationship for analogs of 4-(3-bromoanilino)-6,7-dimethoxyquinazoline (PD 153035), a potent inhibitor of the epidermal growth factor receptor
AUTHOR(S): Bridges, Alexander J.; Zhou, Hairong; Cody, Donna R.; Rewcastle, Gordon W.; McMichael, Amy; Showalter, H. D. Hollis; Fry, David W.; Kraker, Alan J.; Denny, William A.
CORPORATE SOURCE: Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, MI, 48106-1047, USA
SOURCE: Journal of Medicinal Chemistry (1996), 39(1), 267-76
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 124:21051
AB 4-(3-Bromoanilino)-6,7-dimethoxyquinazoline (PD 153035) is a very potent inhibitor (IC50 0.025 nM) of the tyrosine kinase activity of the EGF receptor, binding competitively at the ATP site. Structure-activity relations for close analogs of PD 153035 are very steep. Some derivs. have IC50 ≤80-fold better than predicted from simple additive binding energies, yet analogs possessing combinations of similar Ph and quinazoline substituents do not show this supra-additive effect. Some substituents which are mildly deactivating by themselves can be strongly activating when used in the correct combinations; therefore, certain substituted analogs may induce a change in conformation of the receptor when they bind. There is some bulk tolerance for substitution in the 6- and 7-positions of the quinazoline, so that PD 153035 is not the optimal inhibitor for the induced conformation. 4-(3-Bromoanilino)-6,7-diethoxyquinazoline shows an IC50 of 0.006 nM, making it the most potent inhibitor of the tyrosine kinase activity of the EGF receptor yet reported.

L7 ANSWER 88 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1995:283548 CAPLUS Full-text
DOCUMENT NUMBER: 123:248
TITLE: Tyrosine Kinase Inhibitors. 4. Structure-Activity Relationships among N- and 3-Substituted 2,2'-Dithiobis(1H-indoles) for in vitro Inhibition of Receptor and Nonreceptor Protein Tyrosine Kinases
AUTHOR(S): Palmer, Brian D.; Rewcastle, Gordon W.; Thompson, Andrew M.; Boyd, Maruta; Showalter, H. D. Hollis; Sercel, Anthony D.; Fry, David W.; Kraker, Alan J.; Denny, William A.
CORPORATE SOURCE: School of Medicine, University of Auckland, Auckland, 92019, N. Z.
SOURCE: Journal of Medicinal Chemistry (1995), 38(1), 58-67
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 123:248
AB A series of 3-substituted 2,2'-dithiobis(1H-indoles) were synthesized and evaluated for their ability to inhibit the tyrosine kinase activity of both the epidermal growth factor receptor (EGFR) and the nonreceptor pp60v-src tyrosine kinase, to extend the available structure-activity relationships for this series. The majority of the compds. were prepared either by reaction of 2-chloro-1-methylindole-3-carbonyl chloride with amines, followed by thiomethylation, demethylation, and oxidative dimerization, or by reaction of isocyanates with the anion of 1-methyl-2-indolinethione followed by dimerization. Overall, inhibitory activity is retained by analogs having a wide variety of side chains. A series of 3-carboxamide analogs had moderate to good activity against isolated EGFR (IC50s 1-20 μM), with monoalkyl substitution of the carboxamide being optimal. Polar side chains were generally less effective than lipophilic ones, with benzyl being particularly effective. However, N,N-disubstitution was the most effective pattern for

inhibition of pp60v-src. A variety of substituted N-phenylcarboxamides had lower activity against EGFR than the parent derivative, and a N-thienylcarboxamide also had low activity. A series of 3-ketones, including Me, Ph, and furyl derivs., showed moderate activity against the pp60v-src kinase, but were less effective against EGFR. The mechanism of inhibition of both kinases by these drugs was shown to be noncompetitive with respect to both ATP and peptide substrate. Selected compds. inhibited the growth of Swiss 3T3 cells with IC50s in the low micromolar range and inhibited bFGF-mediated intracellular tyrosine phosphorylation in the same cell line. Thiol inhibits the effects of the compds., suggesting that one possible mechanism of inhibition is thiol-disulfide exchange with thiol-containing residues in the catalytic sites. Crystal structures of two representative compds. show a folded, V-shaped structure, with the disulfide bridge exposed, consistent with this hypothesis.

L7 ANSWER 89 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:695763 CAPLUS Full-text
DOCUMENT NUMBER: 121:295763
TITLE: Inhibition of cyclin-dependent kinases by purine analogs
AUTHOR(S): Vesely, Jaroslav; Havlicek, Libor; Strnad, Miroslav; Blow, J. Julian; Donella-Deana, Arianna; Pinna, Lorenzo; Letham, David S.; Kato, Jun-ya; Detivaud, Lenaick; et al.
CORPORATE SOURCE: Station Biol., Cent. Natl. Recherche Sci., Roscoff, Fr.
SOURCE: European Journal of Biochemistry (1994), 224(2), 771-86
CODEN: EJBCAI; ISSN: 0014-2956
DOCUMENT TYPE: Journal
LANGUAGE: English
AB While testing purines related to the non-specific protein kinase inhibitors N6-dimethyl-aminopurine and N6-(Δ2- isopentenyl)adenine as potential inhibitors of the p34cdc2/cyclin B kinase, we discovered a compound with high specificity, 2-(2-hydroxyethylamino)-6-benzylamino-9-methylpurine (olomoucine). Kinetic anal. of kinase inhibition reveals that olomoucine behaves as a competitive inhibitor for ATP and as a non-competitive inhibitor for histone H1 (linear inhibition for both substrates). The kinase specificity of this inhibition was investigated for 35 highly purified kinases (including p34cdk4/cyclin D1, p40cdk6/cyclin D3, cAMP-dependent and CGMP-dependent kinases, eight protein kinase C isoforms, calmodulin-dependent kinase II, myosin light-chain kinase, mitogen-activated S6 kinase, casein kinase 2, double-stranded RNA-activated protein kinase, AMP-stimulated kinase, eight tyrosine kinases). Most kinases are not significantly inhibited. Only the cell-cycle regulating p34cdc2/cyclin B, p33cdk2/cyclin A and p33cdk2/cyclin E kinases, the brain p33cdk5/p35 kinase and the ERK1/MAP-inase (and its starfish homolog p44mpk) are substantially inhibited by olomoucine (IC50 values are 7, 7, 7, 3 and 25 μM, resp.). The cdk4/cyclin D1 and cdk6/cyclin D3 kinases are not significantly sensitive to olomoucine (IC50 values greater than 1 mM and 150 μM, resp.). N6-(Δ2-Isopentenyl)adenine is confirmed as a general kinase inhibitor with IC50 values of 50-100 μM for many kinases. The purine specificity of cyclin-dependent kinase inhibition was investigated: among 81 purine derivs. tested, only C2, N6 and N9-substituted purines exert a strong inhibitory effect on the p34cdc2/cyclin B kinase. An essentially similar sensitivity to this olomoucine family of compds. was observed for the brain-specific cdk5/p35 kinase. Structure /activity relationship studies allow speculation on the interactions of colomoucine and its analogs with the kinase catalytic subunit. Olomoucine inhibits in vitro M-phase-promoting factor activity in metaphase-arrested Xenopus egg exts., inhibits in vitro DNA synthesis in Xenopus interphase egg exts. and inhibits the licensing factor, an essential replication factor ensuring that DNA is replicated only once in each cell cycle. Olomoucine inhibits the starfish oocyte G2/M transition in vivo. Through its unique selectivity olomoucine provides an anti-mitotic reagent that may preferentially inhibit certain steps of the cell cycle.

L7 ANSWER 90 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:457315 CAPLUS Full-text
DOCUMENT NUMBER: 121:57315
TITLE: Identification of Tricyclic Analogs Related to Ellagic Acid as Potent/Selective Tyrosine Protein Kinase Inhibitors
AUTHOR(S): Dow, Robert L.; Chou, Thomas T.; Bechle, Bruce M.; Goddard, Colin; Larson, Eric R.
CORPORATE SOURCE: Central Research Division, Pfizer Inc., Groton, CT, 06340, USA
SOURCE: Journal of Medicinal Chemistry (1994), 37(14), 2224-31
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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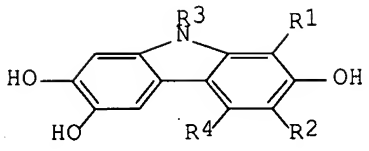

II

AB Tetraphenolic phenanthridinone and carbazole derivs. I and II [R1, R2 = H, OH; R3 = H, Et, CH2Ph, CH2C6H4R-4, CH2C6H3Cl2-3,4, COC6H4r-4,SO2C6H4R-4, 3-pyridylmethyl, (CH2)3Ph, etc.; R = H, NO2, SO2Ph, CN, CF3, Br, Ph, CMe3, SO2Me; R4 = H, Br] related to ellagic acid were prepared and tested for enhanced specificity for inhibition of the tyrosine-specific protein kinase pp60src over other protein kinases. These ring systems were prepared via a general sequence of biaryl bond formation followed by cyclization to form the desired tricyclic ring systems. N-Alkylation, acylation, or sulfonylation and deprotection with BBr3 afforded I and II. Several analogs I and II have potencies comparable to that of ellagic acid and exhibit substantially enhanced selectivities for inhibition of pp60src relative to protein kinase A (PKA), a serine/threonine protein kinase. Carbazole-based analogs II (R1 = OH, R2 = H, R3 = CH2C6H4CN-4, CH2C6H3Cl2-2,6, CH2C6H4SO2Ph) are submicromolar inhibitors of pp60src, with potency for the target tyrosine kinase comparable to that of ellagic acid, however with 2 orders of magnitude greater selectivity vs. that for PKA. As seen for ellagic acid, members of the phenanthridinone-based series, e.g. I (R1 = R3 = H, R2 = OH), exhibited inhibition of pp60src in a manner which is partial mixed noncompetitive with respect to ATP, while carbazole analogs, e.g. II (R1 = R3 = R4 = H, R2 = OH), inhibit pp60src in an ATP competitive manner.

L7 ANSWER 91 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:322877 CAPLUS Full-text
DOCUMENT NUMBER: 120:322877
TITLE: Structure-Activity Relationships in a Series of 5-[(2,5-Dihydroxybenzyl)amino]salicylate Inhibitors of EGF-Receptor-Associated Tyrosine Kinase: Importance of Additional Hydrophobic Aromatic Interactions
AUTHOR(S): Chen, Huixiong; Boiziau, Janine; Parker, Fabienne; Mailliet, Patrick; Commercon, Alain; Tocque, Bruno; Le Pecq, Jean-Bernard; Roques, Bernard-Pierre; Garbay, Christiane
CORPORATE SOURCE: Departement de Pharmacochimie Moleculaire et Structurale, Faculte de Pharmacie, Paris, 75270, Fr.
SOURCE: Journal of Medicinal Chemistry (1994), 37(6), 845-59
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Potent inhibitors of EGF-dependent protein tyrosine kinase (PTK) activity were synthesized in a series of 5-[(2,5-dihydroxybenzyl)amino]salicylates. Several of these compds. inhibited EGF-dependent DNA synthesis in ER 22 cells with IC50 < 1 μM. In this series of PTK inhibitors, the role of the salicylate moiety as a potential divalent ion chelator was tested and found to be nonessential in all cases. The length of the substituting carboxyl group were investigated to improve cellular bioavailability, and this anal. provided compds. with increased inhibitory effect on EGF-induced DNA synthesis. Salicylates esterified with long hydrophobic chains were noncompetitive inhibitors of ATP, in contrast to the free acid and Me salicylate. Moreover, all the tested inhibitors were shown to be noncompetitive inhibitors of the peptide substrate. Structure-activity relationships allowed the authors to suspect a hydrophobic pocket in the tyrosine kinase domain, preferentially interacting with aromatic rings. Finally, the selectivity of the best inhibitors was tested against other kinases, and they were selective for tyrosine kinase. They were also good inhibitors of EGF-receptor autophosphorylation.

L7 ANSWER 92 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:315151 CAPLUS Full-text
DOCUMENT NUMBER: 120:315151
TITLE: A specific inhibitor of phosphatidylinositol 3-kinase, 2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one (LY294002)
AUTHOR(S): Vlahos, Chris J.; Matter, William F.; Hui, Kwan Y.; Brown, Raymond F.
CORPORATE SOURCE: Lilly Res. Lab., Indianapolis, IN, 46285-0403, USA

SOURCE: Journal of Biological Chemistry (1994), 269(7), 5241-8
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Phosphatidylinositol (PtIns) 3-kinase is an enzyme implicated in growth factor signal transduction by associating with receptor and nonreceptor tyrosine kinases, including the platelet-derived growth factor receptor. Inhibitors of PtdIns 3-kinase could potentially give a better understanding of the function and regulatory mechanisms of the enzyme. Quercetin, a naturally occurring bioflavonoid, was previously shown to inhibit PtdIns 3-kinase with an IC50 of 1.3 μg/mL (3.8 μM); inhibition appeared to be directed at the ATP-binding site of the kinase. Analogs of quercetin were investigated as PtdIns 3-kinase inhibitors, with the most potent ones exhibiting IC50 values in the range of 1.7-8.4 μg/mL. In contrast, genistein, a potent tyrosine kinase inhibitor of the isoflavone class, did not inhibit PtdIns 3- kinase significantly (IC50 > 30 μg/mL). Since quercetin has also been shown to inhibit other PtdIns and protein kinases, other chromones were evaluated as inhibitors of PtdIns 3- kinase without affecting PtdIns 4-kinase or selected protein kinases. One such compound, 2-(4-morpholinyl)-8-phenyl-4H- 1-benzopyran-4-one (also known as 2-(4-morpholinyl)-8-phenylchromone, LY294002), completely and specifically abolished PtdIns 3-kinase activity (IC50 = 0.43 μg/mL; 1.40 μM) but did not inhibit PtdIns 4-kinase or tested protein and lipid kinases. Analogs of LY294002 demonstrated a very selective structure- activity relationship, with slight changes in structure causing marked decreases in inhibition. LY294002 was shown to completely abolish PtdIns 3-kinase activity in fMet-Leu-Phe-stimulated human neutrophils, as well as inhibit proliferation of smooth muscle cells in cultured rabbit aortic segments. Since PtdIns 3-kinase appears to be centrally involved with growth factor signal transduction, the development of specific inhibitors against the kinase may be beneficial in the treatment of proliferative diseases as well as in elucidating the biol. role of the kinase in cellular proliferation and growth factor response.

L7 ANSWER 93 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:59455 CAPLUS Full-text
DOCUMENT NUMBER: 118:59455
TITLE: Synthesis and biological evaluation of a series of flavones designed as inhibitors of protein tyrosine kinases
AUTHOR(S): Cunningham, Bernadette D. M.; Threadgill, Michael D.; Groundwater, Paul W.; Dale, Ian L.; Hickman, John A.
CORPORATE SOURCE: Oncogene Sci. Inc., Uniondale, NY, 11553, USA
SOURCE: Anti-Cancer Drug Design (1992), 7(5), 365-84
CODEN: ACDDEA; ISSN: 0266-9536
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of flavones has been prepared, which are variously substituted in the 3,3',4',5 and 7 positions with halo-, alkoxy-, nitro-, amino-, hydroxy-, acyloxy- and azido-groups, for evaluation of their cytotoxicity to ANN-1 cells (3T3 murine fibroblasts transformed with the Abelson murine leukemia virus) which contain a tyrosine kinase. This cytotoxicity was compared to that for their non-transformed 3T3 counterparts. 3'-Amino-4'-methoxyflavone was the most cytotoxic compound (IC50 = 1.6 μM) and was less inhibitory to the non-transformed parent 3T3 cell line (IC50 = 8 μM). The compound was inactive at 50 μM in assays of the inhibition of the cell-associated Abelson protein tyrosine kinase but inhibited an epidermal growth factor (EGF) protein tyrosine kinase by 42% at 50 μM. Quercetin was the most potent inhibitor of the Abelson protein tyrosine kinase but showed no selective inhibition of the growth of ANN-1 cells compared to the parent 3T3 cell line. Different structure- activity relationships were observed between the results of the cytotoxicity assays and inhibition of protein tyrosine kinases . Inhibitors of the Abelson protein tyrosine kinase which were competitive with respect to ATP showed different potencies for inhibition of the epidermal growth factor receptor kinase.

L7 ANSWER 94 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1992:584263 CAPLUS Full-text
DOCUMENT NUMBER: 117:184263
TITLE: The inhibition of phosphatidylinositol 3-kinase by quercetin and analogs
AUTHOR(S): Matter, William F.; Brown, Raymond F.; Vlahos, Chris J.
CORPORATE SOURCE: Lilly Res. Lab., Indianapolis, IN, 46285-0403, USA
SOURCE: Biochemical and Biophysical Research Communications (1992), 186(2), 624-31
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Phosphatidylinositol (PtdIns) 3-kinase is an enzyme involved in cellular responses to growth factors. Quercetin (2-(3,4-dihydroxyphenyl)- 3,5,7-trihydroxy-4H-1-benzopyrano-4-one), a naturally occurring bioflavinoid, was found to inhibit PtdIns 3-kinase with an IC50 of 1.3 μg/mL

(3.8 μM); inhibition appears to be directed towards the ATP binding site of the kinase. Analogs of quercetin were also investigated as PtdIns 3-kinase inhibitors, with the most potent compds. exhibiting IC50's in the range of 1.7-8.4 μg/mL (5-19 μM). In contrast, genistein, a potent tyrosine kinase inhibitor of the isoflavone class, did not inhibit PtdIns 3-kinase significantly (IC50 > 30 μg/mL). These findings suggest that flavinoids may serve as potent inhibitors of PtdIns 3-kinase. Furthermore, the enzyme is much more sensitive to substituents at the 3-position of the flavinoid ring than are other protein and PtdIns kinases, suggesting that specific inhibitors of PtdIns 3-kinase can be developed to explore the biol. role of the enzyme in cellular proliferation and growth factor response.

L7 ANSWER 95 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1992:168772 CAPLUS Full-text
DOCUMENT NUMBER: 116:168772
TITLE: Benzimidazole nucleoside analogs as inhibitors of plant (maize seedling) casein kinases
AUTHOR(S): Dobrowolska, Grazyna; Muszynska, Grazyna; Shugar, David
CORPORATE SOURCE: Inst. Biochem. Biophys., Pol. Acad. Sci., Warsaw, 02-532, Pol.
SOURCE: Biochimica et Biophysica Acta, Protein Structure and Molecular Enzymology (1991), 1080(3), 221-6
CODEN: BBAEDZ; ISSN: 0167-4838
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Halogeno benzimidazole and benzimidazole nucleoside analogs were screened for inhibitory activity vs. purified plant (maize seedling) casein kinase (CK) I, IIA, and IIB, and the results compared with those previously reported for some of the compds. as inhibitors of the corresponding mammalian CK-1 and CK-2. One new analog, the riboside of 5,7-dibromobenzimidazole, which is sterically constrained to the anti conformation about the glycosidic bond, and is a good inhibitor, exhibited appreciable (5-7-fold) discrimination between the type I and type II enzymes. An increase in the number of halogen substituents on the benzene ring of benzimidazole from 2 to 3 led to marked enhancement of inhibitory activity, particularly against the type II enzymes, with a decrease in Ki from 24 to 4 μM. The 2-aza analog of 5,6-dichlorobenzimidazole, i.e., 5,6-dichlorobenzotriazole, as the free base, even more effectively discriminated between the 2 types of plant casein kinases, with Ki ≈ 100 μM for CK-I, and Ki ≈ 9 μM for CK-IIA and CK-IIB. Inhibition in all instances was competitive with respect to ATP (for CK-I) and ATP and GTP (for CK-IIA and CK-IIB). The results are compared with those for halogenated isoquinolinesulfonamide inhibitors previously reported, leading to proposals for the synthesis of potentially more effective and more discriminating inhibitors. Attention is drawn to the significant role of the halogen substituents in the mechanism(s) of action of the structurally related benzimidazole, benzotriazole, and naphthalene and isoquinoline, inhibitors of protein kinases.

L7 ANSWER 96 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1992:120373 CAPLUS Full-text
DOCUMENT NUMBER: 116:120373
TITLE: Structure-activity relationships of phenothiazines and related drugs for inhibition of protein kinase C
AUTHOR(S): Aftab, Dana T.; Ballas, Lawrence M.; Loomis, Carson R.; Hait, William N.
CORPORATE SOURCE: Sch. Med., Yale Univ., New Haven, CT, 06510, USA
SOURCE: Molecular Pharmacology (1991), 40(5), 798-805
CODEN: MOPMA3; ISSN: 0026-895X
DOCUMENT TYPE: Journal
LANGUAGE: English
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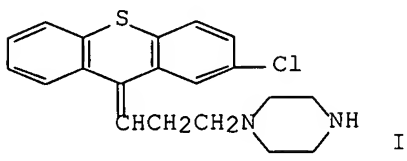

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AB Phenothiazines are known to inhibit the activity of protein kinase C. To identify structural features that determine inhibitory activity against the enzyme, the authors utilized a

semiautomated assay to compare the potency of >50 phenothiazines and related compds. Potency was decreased by trifluoro substitution at position 2 on the phenothiazine nucleus and increased by quinoid structures on the nucleus. An alkyl bridge of at least 3 carbons connecting the terminal amine to the nucleus was required for activity. Primary amines and unsubstituted piperazines were the most potent amino side chains. 7,8-Dihydroxychloropromazine (DHCP) (IC50 = 8.3 μM) and N 751 (I) (IC50 = 14 μM) were selected for further study because of their potency and distinct structural features. Under standard (vesicle) assay conditions, DHCP was noncompetitive with respect to phosphatidylserine and a mixed-type inhibitor with respect to ATP. I was competitive with respect to phosphatidylserine and noncompetitive with respect to ATP. Using the mixed micelle assay, DHCP was a competitive inhibitor with respect to both phosphatidylserine and ATP. DHCP was selective for protein kinase C compared with cAMP-dependent protein kinase, calmodulin-dependent protein kinase type II, and casein kinase. I was more potent against protein kinase C compared with cAMP-dependent protein kinase and casein kinase but less potent against protein kinase C compared with calmodulin-dependent protein kinase type II. DHCP was analyzed for its ability to inhibit different isoenzymes of protein kinase C, and no significant isoenzyme selectivity was detected. These data provide important information for the rational design of more potent and selective inhibitors of protein kinase C.

L7 ANSWER 97 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:674290 CAPLUS Full-text
DOCUMENT NUMBER: 115:274290
TITLE: The bisindolylmaleimide GF 109203X is a potent and selective inhibitor of protein kinase C
AUTHOR(S): Toullec, Dominique; Pianetti, Pascal; Coste, Herve; Bellevergue, Patrice; Grand-Perret, Thierry; Ajakane, Myriam; Baudet, Valerie; Boissin, Patrick; Boursier, Eric; et al.
CORPORATE SOURCE: Cent. Rech., Lab. Glaxo, Les Ulis, 91951, Fr.
SOURCE: Journal of Biological Chemistry (1991), 266(24), 15771-81
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Staurosporine is the most potent inhibitor of protein kinase C (PKC) described in the literature with a half-maximal inhibitory concentration (IC50) of 10 nM. Nevertheless, this natural product is poorly selective when assayed against other protein kinases. To obtain specific PKC inhibitors, a series of bisindolylmaleimides has been synthesized. Structure-activity relationship studies allowed the determination of the substructure responsible for conferring high potency and lack of selectivity in the staurosporine mol. Several aminoalkyl bisindolylmaleimides were found to be potent and selective PKC inhibitors (IC50 values from 5 to 70 nM). Among these compds. GF 109203X has been chosen for further studies aiming at the characterization of this chemical family. GF 109203X was a competitive inhibitor with respect to ATP (Ki = 14 nM) and displayed high selectivity for PKC as compared to five different protein kinases. The potency and specificity of GF 109203X was further determined in 2 cellular models: human platelets and Swiss 3T3 fibroblasts. GF 109203X efficiently prevented PKC-mediated phosphorylations of an Mr = 47,000 protein in platelets and of an Mr = 80,000 protein in Swiss 3T3 cells. In contrast, in the same models, the PKC inhibitor failed to prevent PKC-independent phosphorylations. GF 109203X inhibited collagen- and α-thrombin- induced platelet aggregation as well as collagen-triggered ATP secretion. However, ADP-dependent reversible aggregation was not modified. In Swiss 3T3 fibroblasts, GF 109203X reversed the inhibition of EGF binding induced by phorbol 12,13-dibutyrate and prevented [3H]thymidine incorporation into DNA, only when this was elicited by growth promoting agents which activate PKC. These results illustrate the potential of GF 109203X as a tool for studying the involvement of PKC in signal transduction pathways.

L7 ANSWER 98 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:484825 CAPLUS Full-text
DOCUMENT NUMBER: 115:84825
TITLE: Sulfonylbenzoyl-nitrostyrenes: Potential bisubstrate type inhibitors of the EGF-receptor tyrosine protein kinase
AUTHOR(S): Traxler, Peter M.; Wacker, Oskar; Bach, Ha L.; Geissler, Johanna F.; Kump, Wilhelm; Meyer, Thomas; Regenass, Urs; Roesel, Johannes L.; Lydon, Nicholas
CORPORATE SOURCE: Oncol. Virol. Res. Dep., Ciba-Geigy, Ltd., Basel, CH-4002, Switz.
SOURCE: Journal of Medicinal Chemistry (1991), 34(8), 2328-37
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 115:84825
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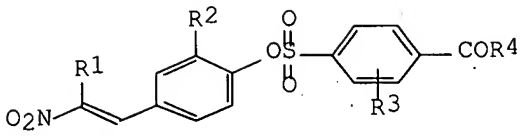


I, R1=R2=R3=H, R4=OH
II, R1=R2=R3=H, R4=adamantyl
III, R1=R2=R3=H, R4=NHMe
IV, R1=R2=H, R3=2-OH, R4=OH

AB The synthesis and biol. activities of a series of sulfonylbenzoylnitrostyrene derivs. as a novel class of selective bisubstrate type inhibitors of the EGF-receptor tyrosine protein kinase is described. The most potent derivs. inhibited the EGF-R tyrosine kinase with angiotensin II as exogenous substrate with IC50 values of ≤1 μM. No inhibition of the v-abl tyrosine kinase and the serine/threonine kinases PKC and PK-A was observed In addition, active derivs. (I and II) effectively blocked the autophosphorylation of the EGF-R in vitro. Starting from the acids such as I, a series of esters, amides, and peptides was synthesized with the aim of increasing cellular penetration. Several amides showed potent antiproliferative effects using the EGF-dependent Balb/MK mouse epidermal keratinocyte cell line. Addnl., with the amide III inhibition of EGF-R autophosphorylation was demonstrated in a EGF-dependent A431 cell line. Computer assisted mol. modeling studies by using a computer-generated model for the transition state of the γ-phosphoryl transfer from ATP to a tyrosine moiety and fitting expts. using the highly potent derivative IV (IC50 value = 54 nM) support the hypothesis that the sulfonylbenzoyl group mimics a diphosphate moiety in the transition state. The rational design of tyrosine kinase inhibitors using the inhibitory nitrostyrene moiety as a tyrosine mimic together with the sulfonylbenzoyl moiety as a diphosphate mimic leads to highly potent and selective multisubstrate type inhibitors.

L7 ANSWER 99 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:141353 CAPLUS Full-text
DOCUMENT NUMBER: 114:141353
TITLE: Sphingosine inhibits phosphatidate phosphohydrolase in human neutrophils by a protein kinase C-independent mechanism
AUTHOR(S): Mullmann, Theodore J.; Siegel, Marvin I.; Egan, Robert W.; Billah, M. Motasim
CORPORATE SOURCE: Dep. Allergy Immunol., Schering-Plough Res., Bloomfield, NJ, 07003, USA
SOURCE: Journal of Biological Chemistry (1991), 266(4), 2013-16
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Human neutrophils have been labeled in 1-O-alkylphosphatidylcholine with 3H in both the alkyl chain and the choline moiety. Upon stimulation of these labeled cells with formyl-Met-Leu-Phe, C5a, or phorbol 12-myristate 13-acetate, phospholipase D is activated to produce 1-O-[3H]alkylphosphatidic acid ([3H]alkyl-PA) and [3H]choline. The [3H]alkyl-PA is then dephosphorylated by phosphatidate phosphohydrolase (PPH) to produce 1-O-[3H]alkyldiglyceride ([3H]alkyl-DG). Sphingosine, a sphingoid base known to inhibit protein kinase C (PKC), causes a dose-dependent inhibition of [3H]alkyl-DG formation. This inhibition is accompanied by increased accumulation of [3H]alkyl-PA without alterations in [3H]choline formation. Studies using various other sphingoid bases demonstrate that a long hydrocarbon chain and an amino group are required for the inhibition of DG formation. These results suggest that sphingoid bases inhibit PPH activity without altering phospholipase D activation and that they exhibit a similar structure-activity relationship for both PPH and PKC. K252a, a PKC inhibitor which acts by competing for ATP binding sites, does not inhibit the formation of [3H]alkyl-DG, [3H]alkyl-PA, or [3H]choline at a concentration (3 μM) that completely blocks phorbol 12-myristate 13-acetate-induced protein phosphorylation. Moreover, in neutrophil homogenates, sphingosine but not octylamine, inhibits PPH activity in a dose-dependent manner. Thus sphingosine inhibits PPH activity by a PKC-independent mechanism, raising the possibility that sphingoid bases may play a role in regulating PPH-mediated lipid metabolism in stimulated cells.

L7 ANSWER 100 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:94645 CAPLUS Full-text
DOCUMENT NUMBER: 114:94645

TITLE: MDL 27,032 [4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone], an active site-directed inhibitor of protein kinase C and cyclic AMP-dependent protein kinase that relaxes vascular smooth muscle

AUTHOR(S): Robinson, Phillip J.; Cheng, Hsien C.; Black, Christine K.; Schmidt, Christopher J.; Kariya, Takashi; Jones, Winton D.; Dage, Richard C.

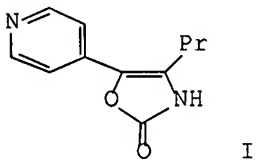
CORPORATE SOURCE: Merrell Dow Res. Inst., Cincinnati, OH, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics (1990), 255(3), 1392-8
CODEN: JPETAB; ISSN: 0022-3565

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



I

AB MDL 27,032 [4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone] (I) is a novel vasodilator whose mechanism of action has not been elucidated. Whether smooth muscle relaxation by MDL 27,032, in vitro, may involve an alteration in the activity of protein kinase C, cAMP (cCMP)-dependent protein kinase or myosin light chain kinase were determined investigating the effects of MDL 27,032 on cyclic nucleotide phosphodiesterases (PDEs) and protein kinase activities. Strips of dog femoral artery or saphenous vein contracted with phorbol 12-myristate 13-acetate (PMA) were relaxed by 100 μM concns. of MDL 27,032, as well as by other known inhibitors of PDEs [3-isobutyl-1-methylxanthine and papaverine], myosin light chain kinase (W-7) and protein kinase C (H-7 and polymyxin B). In contrast to 3-isobutyl-1-methylxanthine and papaverine, MDL 27,032 was either inactive or weak as an inhibitor of purified PDE types, I, II, IVa and IVb. Similarly, it was a weak inhibitor of myosin light chain kinase. However, MDL 27,032 was a significantly more potent inhibitor of protein kinase C and cAMP-dependent protein kinase in cytosolic exts. of dog vein. Kinetic expts. utilizing purified rat brain protein kinase C revealed that inhibition with MDL 27,032 was competitive with Mg++- ATP (Ki 24 μM) and noncompetitive with phospholipid, diacylglycerol, PMA, calcium or substrate proteins. Inhibition of the catalytic subunit of cAMP-dependent protein kinase was also competitive with Mg++-ATP (Ki 14.3 μM). Similar results were obtained with MDL 27,032 and H-7 on both enzymes. MDL 27,032 and H-7 also inhibited PMA-induced phosphorylation of the 40 kDa phosphoprotein in intact human platelets prelabeled with 32Pi at similar concns. The data indicate that MDL 27,032 is a potent active site-directed inhibitor of protein kinase C and cAMP-dependent protein kinase. Inhibition of protein kinase C may be the mechanism by which MDL 27,032 relaxes smooth muscle.

L7 ANSWER 101 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1991:19969 CAPLUS Full-text

DOCUMENT NUMBER: 114:19969

TITLE: A rationale for the design of an inhibitor of tyrosyl kinase

AUTHOR(S): Yuan, Chiun Jye; Jakes, Scott; Elliott, Shirley; Graves, Donald J.

CORPORATE SOURCE: Dep. Biochem. Biophys., Iowa State Univ., Ames, IA, 50011, USA

SOURCE: Journal of Biological Chemistry (1990), 265(27), 16205-9
CODEN: JBCHA3; ISSN: 0021-9258

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Two gastrin analogs containing a D- and a L-tetrafluorinated tyrosyl residue (Arg-Arg-Leu-Glu-Glu-Glu-Glu-Glu-Ala-(F4)Tyr-Gly) were synthesized and tested as substrates and inhibitors of insulin receptor kinase. No phosphorylation of these peptides was observed, but both gastrin analogs were effective inhibitors in the micromolar range. Although the D- and L-tetrafluorotyrosine-gastrin analogs differed in the sequence by only 1 amino acid residue, a different inhibitory pattern was obtained with the insulin receptor. The inhibition of the all-L-isomer was competitive with respect to both the protein substrate, reduced, S-carboxymethylated, and maleylated lysozyme (RCMM-lysozyme), and ATP with a Ki of 4 μM. This result corroborated a previous finding that the

kinetic mechanism for insulin receptor was a random Bi Bi mechanism. Different from the L-isomer, the D-analog was competitive with RCMM-lysozyme and noncompetitive toward ATP and gave an apparent Ki of 20 μM. Free tetrafluorotyrosine also showed competitive inhibition with the protein substrate, RCMM-lysozyme (Ki = 18 mM), whereas free tyrosine showed no effect on the activity of insulin receptor. These results show the importance of the charge state and nucleophilicity of the phenolic component in substrate recognition and catalysis and provide a rationale for the design of inhibitors of tyrosyl phosphorylation.

L7 ANSWER 102 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:454868 CAPLUS Full-text
DOCUMENT NUMBER: 113:54868
TITLE: Nucleoside inhibitors of rhodopsin kinase
AUTHOR(S): Palczewski, Krzysztof; Kahn, Nikhat; Hargrave, Paul A.
CORPORATE SOURCE: Dep. Ophthalmol., Univ. Florida, Gainesville, FL, 32610, USA
SOURCE: Biochemistry (1990), 29(26), 6276-82
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The specificity of the ATP-binding site of rhodopsin kinase was studied with adenosine analogs that are competitive inhibitors. Systematic changes in the ribose ring (position 5') and the purine ring (positions 2, 6, 7, 8, and 9) and determination of the inhibitory properties of these analogs lead to the following conclusions. The N6 in the purine ring is essential for binding at the active site, which may explain the marked preference for ATP rather than GTP as substrate. The configuration of the sugar moiety is critical for the binding. Positions 2, 3, and 8 of the purine ring, as well as the polyphosphate chain, play a minor role in substrate recognition by rhodopsin kinase. ATP.gamma.S is a good substrate for rhodopsin kinase (thus rhodopsin phosphorothioate, a phosphatase-resistant product, can be formed in order to study the role of phosphorylation in rod outer segments). Pyrrolopyrimidine derivs. are very potent inhibitors of rhodopsin kinase. The Ki of one of these, sangivamycin, is 180 nM. Sangivamycin in solution assumes the anti conformation, as determined by nuclear Overhauser measurement. These measurements show that the most potent inhibitors of rhodopsin kinase, sangivamycin and toyocamycin, occur in solution preferentially in the anti conformation. Many nucleotides and nucleosides tested that are not inhibitors are syn, and many that are inhibitors form a mixture of syn and anti. The hypothesis that inhibitors may have a conformation intermediate between syn and anti was strengthened by testing a cyclic nucleoside locked in an anti conformation. This compound, a 8,3'-cycloadenosine derivative, is a good inhibitor of rhodopsin kinase with Ki = 10 μM. This suggests that rhodopsin kinase binds nucleosides in an intermediate syn/anti conformation. The low Ki value for sangivamycin allowed for the blocking of phosphorylation in whole rod outer segments with submicromolar concns., lower than those required for blocking other protein kinases.

L7 ANSWER 103 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:174609 CAPLUS Full-text
DOCUMENT NUMBER: 112:174609
TITLE: Ribofuranosyl-benzimidazole derivatives as inhibitors of casein kinase-2 and casein kinase-1
AUTHOR(S): Meggio, Flavio; Shugar, David; Pinna, Lorenzo A.
CORPORATE SOURCE: Dep. Biol. Chem., Univ. Padova, Padua, I-35131, Italy
SOURCE: European Journal of Biochemistry (1990), 187(1), 89-94
CODEN: EJBCAI; ISSN: 0014-2956
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 5,6-Dichloro-1-(β-D-ribofuranosyl)benzimidazole (DiCl-RB) is a powerful inhibitor of casein kinase-2 (CK-2). Here a series of 17 analogs of DiCl-RB has been employed for studying the specificity and the mode of action of this family of CK-2 inhibitors. The 2 halogen substituents on the benzene ring are shown to play a prominent role in inhibition, the 5,6-dibromo derivative (DiBr-RB) being 5-fold more effective than DiCl-RB (Ki = 2 μM cf. 10 μM, with GTP as substrate), whereas the difluoro derivative (DiF-RB) is nearly as ineffective as unsubstituted 1-(β-D-ribofuranosyl)benzimidazole. On the other hand, although some modifications of the ribose group significantly decrease the inhibitory efficiency, the sugar moiety is not strictly required, since dichlorobenzimidazole (DiCl-Bz) itself is an inhibitor almost as good as DiCl-RB. Inhibition of CK-2 by DiCl-RB and by its analogs, DiCl-Bz included, is of the competitive type with respect to the nucleotide substrate, the Ki values being lower with GTP than with ATP. The Ki values of the most potent inhibitor, DiBr-RB, with ATP and GTP, are 6 and 2 μM, resp., denoting an affinity for the enzyme higher than that of the physiol. substrates, ATP and GTP. DiBr-RB has been assayed for its inhibitory capacity toward several protein kinases other than CK-2. Protein kinase C, cAMP-dependent protein kinase, the Ser/Thr protein kinase expressed by pseudorabies virus, and 4 different tyrosine protein kinases from spleen proved insensitive to DiBr-RB concns. capable of almost entirely suppressing the activity of rat liver and maize seedling CK-2. Casein kinase-1,

however, is nearly as sensitive as CK-2 to DiBr-RB. Inhibition of CK-1 is also of the competitive type with respect to ATP (Ki = 14 μM). Although the inhibitory spectrum of CK-1 by the various analogs is reminiscent of that observed with CK-2, a remarkable difference is revealed by 5'-phosphorylation of ribose which increases the Ki with CK-2 while decreasing that with CK-1.

L7 ANSWER 104 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:111504 CAPLUS Full-text
DOCUMENT NUMBER: 112:111504
TITLE: Isolation of a novel tyrosine kinase inhibitor, lavendustin A, from Streptomyces griseolavendus
AUTHOR(S): Onoda, Toshihiko; Iinuma, Hironobu; Sasaki, Yumi; Hamada, Masa; Isshiki, Kunio; Naganawa, Hiroshi; Takeuchi, Tomio; Tatsuta, Kuniaki; Umezawa, Kazuo
CORPORATE SOURCE: Inst. Microbial Chem., Tokyo, 141, Japan
SOURCE: Journal of Natural Products (1989), 52(6), 1252-7
CODEN: JNPRDF; ISSN: 0163-3864
DOCUMENT TYPE: Journal
LANGUAGE: English
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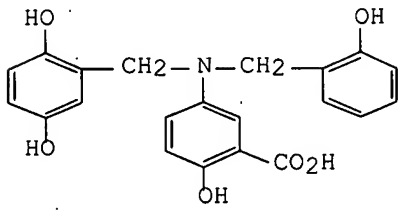

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AB A potent tyrosine kinase inhibitor, lavendustin A (I), has been isolated from a Bu acetate extract of S. griseolavendus culture filtrate. It inhibits epidermal growth factor receptor-associated tyrosine kinase with a IC50 of 4.4 ng/mL, which is about 50 times more inhibitory than erbstatin. It does not inhibit protein kinase A or C. Its structure, determined by spectral data and total synthesis, is novel, having a tertiary amine in the center with substituted benzyl and Ph groups. Lavendustin A competes with ATP and is noncompetitive with the peptide. The structure-activity relationships of lavendustin derivs. are discussed.

L7 ANSWER 105 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1989:566798 CAPLUS Full-text
DOCUMENT NUMBER: 111:166798
TITLE: Inhibitory effects of the tyrosine kinase inhibitor genistein on mammalian DNA topoisomerase II
AUTHOR(S): Markovits, Judith; Linassier, Claude; Fosse, Philippe; Couprie, Jeanine; Pierre, Josiane; Jacquemin-Sablon, Alain; Saucier, Jean Marie; Le Pecq, Jean Bernard; Larsen, Annette K.
CORPORATE SOURCE: Lab. Pharmacol. Mol., Inst. Gustave Roussy, Villejuif, 94805, Fr.
SOURCE: Cancer Research (1989), 49(18), 5111-17
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tyrosine phosphorylation plays a crucial role in cell proliferation and transformation which suggests that tyrosine kinase-specific inhibitors might be used as anticancer agents. The cytotoxic effect of the potent tyrosine kinase inhibitor genistein was studied in various cell lines. 9-Hydroxyellipticine- resistant Chinese hamster lung cells (DC-3F/9-OH-E) were markedly more resistant to genistein than the parental cell line (DC-3F). The DC-3F/9-OH-E cells had an altered DNA topoisomerase II activity. The effects of genistein on DNA topoisomerase II-related activities were examined in nuclear exts. from DC-3F cells and purified DNA topoisomerase II from calf thymus. Genistein inhibited the decatenation activity of DNA topoisomerase II and stimulated DNA topoisomerase II-mediated double strand breaks in pBR322 DNA on sites different from those of 4'-(9-acridinylamino)methanesulfonyl-m-anisidide, etoposide, and 2-methyl-9-hydroxyellipticinium. Structure-activity studies with 6 chemical related compds. showed that only genistein has an effect on the cleavage activity of DNA topoisomerase II in the concentration range studied.

Genistein treatment of DC-3F cells caused protein-linked DNA strand breaks as shown by DNA filter elution. Viscosimetric (lengthening) studies demonstrated that genistein is not a DNA intercalator. Genistein is an interesting compound because it induces cleavable complexes without intercalation. Thus, genistein is an inhibitor of both protein tyrosine kinases and mammalian DNA topoisomerase II. This could be explained by sharing of a common amino acid sequence between the 2 proteins at the ATP-binding site.

L7 ANSWER 106 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1989:473633 CAPLUS Full-text
DOCUMENT NUMBER: 111:73633
TITLE: Protein kinase C inhibition by plant flavonoids. Kinetic mechanisms and structure -activity relationships
AUTHOR(S): Ferriola, Patrice C.; Cody, Vivian; Middleton, Elliott, Jr.
CORPORATE SOURCE: Dep. Med., State Univ. New York, Buffalo, NY, 14203, USA
SOURCE: Biochemical Pharmacology (1989), 38(10), 1617-24
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Protein kinase C (PKC) from rat brain was inhibited by plant flavonoids in a concentration-dependent manner depending on flavonoid structure. Of the 15 flavonoids studied, fisetin, quercetin and luteolin were the most potent, whereas hesperetin, taxifolin and rutin were among the least potent. Fisetin was almost 100% inhibitory at a concentration of 100 μM. The extent of inhibition was the same whether diacylglycerol or 12-O-tetradecanoylphorbol-13-acetate was used as enzyme activator. The inhibition was independent of Ca2+, phospholipid, and enzyme activator, as shown by inhibition of protamine phosphorylation in the absence of the regulatory components. Fisetin was a competitive inhibitor with respect to ATP binding and noncompetitive with respect to protein substrate. X-ray crystal structure anal. of hesperetin monohydrate showed that the mol. is essentially planar despite the sofa conformation of the γ-pyran ring and the 27° twist of the 2-Ph ring. Comparison of this inactive flavanone with those of the active flavones showed that, although hesperetin can adopt a planar profile similar to those of fisetin and quercetin, the 4'-methoxy substituent blocks an essential structural feature required for inhibitory activity. Anal. of these structure-activity data revealed a model of the minimal essential features required for PKC inhibition by flavonoids: a coplanar flavone structure with free OH substituents at the 3', 4' and 7-positions.

L7 ANSWER 107 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1989:53552 CAPLUS Full-text
DOCUMENT NUMBER: 110:53552
TITLE: Molecular mechanism of the inhibitory effects of isoquinolinesulfonamides on protein kinases
AUTHOR(S): Hagiwara, Masatoshi
CORPORATE SOURCE: Sch. Med., Mie Univ., Tsu, 514, Japan
SOURCE: Mie Medical Journal (1988), 38(2), 137-53
CODEN: MMJJAI; ISSN: 0026-3532
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mol. properties of myosin light-chain (MLC)-kinase, protein kinase C, and cAMP-dependent protein kinase were analyzed using isoquinolinesulfonamide derivs. as selective inhibitors. These protein kinases were potently inhibited by 1-(8-chloro-5-isoquinolinesulfonyl) piperazine (HA-156) and its derivs. Kinetic anal. indicated that HA-156 inhibited the 2 former enzymes competitively with respect to ATP, and Ki values of HA-156 for MLC-kinase and protein kinase C were 7.3 and 7.2 μM, resp. To clarify mol. mechanisms of the isoquinolinesulfonamides to inhibit the Ca2+-dependent protein kinases, the structure-activity relationships of HA-156 and its derivs. were examined The dechlorinated analogs, HA-100 and HA-142, markedly decreased the affinity for MLC-kinase, suggesting that the inhibitory effect of isoquinolinesulfonamide derivs. depends upon the hydrophobicity of the compds. There is a good correlation between MLC-kinase inhibition and hydrophobicity determined by reverse-phase chromatog. In contrast, HA-140 and HA-142 showed weak inhibition of protein kinase C, suggesting that the electron d. of the N in the isoquinoline ring of the compds. correlates with the potency to inhibit protein kinase C activity. When the piperazine ring was replaced by the methylaminoethyl chain, the compound, named H-8, specifically inhibited cyclic nucleotide-dependent protein kinases and did not affect Ca2+-dependent enzymes. The interaction of H-8 with the catalytic subunit of cAMP-dependent protein kinase was studied, using various affinity-labeling reagents of the ATP -binding site of the purified protein kinase catalytic subunit and the gel permeation binding assay. The data showed that H-8 specifically binds to the ATP-binding site of the catalytic subunit with a binding ratio of 1:1 and that H-8 has unique features which differ from the ATP analogs, in the following points: (a) H-8, among other protein kinases or ATP utilizing enzymes, specifically inhibits cyclic nucleotide-dependent protein kinase ; (b) the binding constant (Km) of H-8 to the enzyme is much lower than that of ATP; (c) the binding of H-8 to the enzyme is independent of Mg2+; (d) the binding subsite of H-8 of the active site of the enzyme slightly differs from that of ATP. These isoquinolinesulfonamide

derivs. should prove to be useful tools for distinguishing the role of each protein kinase, in vivo.

L7 ANSWER 108 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1988:522004 CAPLUS Full-text
DOCUMENT NUMBER: 109:122004
TITLE: Differential effects of flavonoids as inhibitors of tyrosine protein kinases and serine/threonine protein kinases
AUTHOR(S): Hagiwara, Masatoshi; Inoue, Shigeo; Tanaka, Toshio; Nunoki, Kazuo; Ito, Masaaki; Hidaka, Hiroyoshi
CORPORATE SOURCE: Sch. Med., Mie Univ., Mie, 514, Japan
SOURCE: Biochemical Pharmacology (1988), 37(15), 2987-92
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The inhibitory potencies of bioflavonoids toward various tyrosine protein kinases and serine/threonine protein kinases were investigated. The phosphotransferase activity of an oncogene product, pp130fps, and a growth factor receptor, insulin receptor, were inhibited by myricetin, a derivative of quercetin. However, tyrosine kinase activity in the particulate fraction from human platelets (PM-TPK) was resistant to myricetin. Apparent Ki values of myricetin for tyrosine protein kinase of pp130fpsand insulin receptor were 1.8 and 2.6 μM, resp. The Ki values for serine/threonine kinase activities of myosin light chain kinase (MLC-kinase), casein kinase I, casein kinase II, cAMP-dependent protein kinase, and protein kinase C were 1.7, 9.0, 0.6, 27.5, and 12.1 μM, resp. Lineweaver-Burk plots revealed that myricetin competitively inhibits pp130fpstyrosine kinase, myosin light chain kinase, and casein kinase I and II with ATP, but does not inhibit other protein kinases. Since myricetin is a hydroxylated derivative of quercetin, the inhibitory effects of a series of 7 flavonoids with various nos. of OH residues were examined Structure activity studies exhibited that the inhibitory potencies of the flavonoids for tyrosine kinase of pp130fpsand insulin receptor correlated with the number of OH residues on the flavone rings, whereas the hydroxylation influenced to a lesser extent the inhibitory potencies for serine/threonine protein kinase. The OH residues at position 3' and 5' did not affect the activities of cAMP-dependent protein kinase, and protein kinase C, and the hydroxylation at position 5' was detrimental for the inhibition of MLC-kinase, and casein kinase I and II. Thus, flavonoids may be useful tools to elucidate the active site of tyrosine and serine/threonine protein kinases.

L7 ANSWER 109 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1987:529803 CAPLUS Full-text
DOCUMENT NUMBER: 107:129803
TITLE: Selective modulation of calcium-dependent myosin phosphorylation by novel protein kinase inhibitors, isoquinolinesulfonamide derivatives
AUTHOR(S): Hagiwara, Masatoshi; Inagaki, Masaki; Watanabe, Masato; Ito, Masaaki; Onoda, Koji; Tanaka, Toshio; Hidaka, Hiroyoshi
CORPORATE SOURCE: Sch. Med., Mie Univ., Tsu, 514, Japan
SOURCE: Molecular Pharmacology (1987), 32(1), 7-12
CODEN: MOPMA3; ISSN: 0026-895X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ca2+-dependent myosin phosphorylation by Ca2+/calmodulin-dependent myosin light chain kinase (MLC-kinase) and protein kinase C were studied using selective inhibitors, isoquinolinesulfonamide derivs. Both protein kinases were potently inhibited by (1-(8-chloro-5-isoquinolinesulfonyl)piperazine (HA-156) and its derivs. Kinetic anal. indicated that HA-156 inhibited both enzymes competitively with respect to ATP, and KI values of HA-156 for MLC-kinase and protein kinase C were 7.3 and 7.2 μM, resp. To clarify mol. mechanisms of the isoquinolinesulfonamides in inhibiting the Ca2+-dependent protein kinases, the structure-activity relationships of HA-156 and its derivs. were examined The dechlorinated analogs, HA-100 and HA-142, markedly decreased the affinity for MLC-kinase, suggesting that the inhibitory effect of isoquinolinesulfonamide derivs. depends upon hydrophobicity of the compds. There is good correlation between MLC-kinase inhibition and hydrophobicity determined by reverse-phase chromatog. In contrast, HA-140 and HA-142 showed weak inhibition of protein kinase C, suggesting that the electron d. of the nitrogen in the isoquinoline ring of the compds. correlates with the potency to inhibit protein kinase C activity. These pairs of isoquinolinesulfonamides will aid in elucidating the biol. roles of Ca2+-dependent myosin phosphorylation in intact cells. HA-156 and HA-140 inhibited myosin light chain phosphorylation in platelets exposed to collagen, whereas HA-142 and HA-100 did not. These isoquinolinesulfonamide derivs. should prove to be useful tools for distinguishing between the biol. functions of Ca2+-activated, phospholipid-dependent, and Ca2+/calmodulin-dependent myosin light chain phosphorylation, in vivo.

L7 ANSWER 110 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1987:419887 CAPLUS Full-text
DOCUMENT NUMBER: 107:19887
TITLE: Genistein, a specific inhibitor of tyrosine-specific protein kinases
AUTHOR(S): Akiyama, Tetsu; Ishida, Junko; Nakagawa, Suguru; Ogawara, Hiroshi; Watanabe, Shunichi; Itoh, Noriki; Shibuya, Masabumi; Fukami, Yasuo
CORPORATE SOURCE: Dep. Biochem., Meiji Coll. Pharm., Tokyo, 154, Japan
SOURCE: Journal of Biological Chemistry (1987), 262(12), 5592-5
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tyrosine-specific protein kinase activity of the EGF receptor, pp60v-src, and pp110gag-fes was inhibited in vitro by an isoflavone, genistein. The inhibition was competitive with respect to ATP and noncompetitive to a phosphate acceptor, histone H2B. By contrast, genistein scarcely inhibited the enzyme activities of serine- and threonine-specific protein kinases, such as cAMP-dependent protein kinase, phosphorylase kinase, and the Ca2+/phospholipid-dependent enzyme protein kinase C. When the effect of genistein on the phosphorylation of the EGF receptor was examined in cultured A431 cells, EGF-stimulated serine, threonine, and tyrosine phosphorylation was decreased. Phosphoamino acid anal. of total cell proteins revealed that genistein inhibited EGF-stimulated increase in phosphotyrosine level in A431 cells.

L7 ANSWER 111 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1983:100752 CAPLUS Full-text
DOCUMENT NUMBER: 98:100752
TITLE: Purification, characterization, substrate and inhibitor specificity of adenosine kinase from several Eimeria species
AUTHOR(S): Miller, Richard L.; Adamczyk, David L.; Rideout, Janet L.; Krenitsky, Thomas A.
CORPORATE SOURCE: Wellcome Res. Lab., Research Triangle Park, NC, 27709, USA
SOURCE: Molecular and Biochemical Parasitology (1982), 6(4), 209-23
CODEN: MBIPDP; ISSN: 0166-6851
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The interactions of ribonucleosides of some pyrazolo[3,4-d]pyrimidines, previously shown to be potent anticoccidial agents, with adenosine kinase [9027-72-9] were studied. The enzyme was purified by affinity chromatog. from the sporulated oocysts of 3 avian coccidia, E. tenella, E. acervulina, and E. brunetti as well as from chicken liver. Comparative studies revealed several differences among the enzymes. Mg appeared not to be an inhibitor of the E. tenella enzyme, but did inhibit the enzymes from the other 3 sources. ATP [56-65-5] In excess of the Mg concentration strongly inhibited the E. brunetti enzyme but had only a small effect on the other enzymes. The chicken liver enzyme utilized a broader variety of triphosphate donors than did any of the enzymes from Eimeria species. ATP, dATP, GTP, dGTP and ITP were the best substrates. Studies with pyrazolo[3,4-d]pyrimidine nucleosides revealed 2 groups of enzymes with similar inhibitor specificities, the chicken liver and E. acervulina vs. the E. tenella and E. brunetti enzyme. This grouping roughly correlates with the in vivo anticoccidial specificity of these compds. Substrate specificity studies using 4-ethylthio- [77975-21-4] and 4-cinnamylthio-1-β-D-ribofuranosylpyrazolo[3,4-d]pyrimidine [84372-83-8], which have shown potent anticoccidial activity in vivo, revealed that each served as a substrate for the enzymes from E. tenella and E. acervulina. The E. tenella enzyme was the more efficient at the phosphorylation of those compds. However, only the ethylthio- compound was detectably phosphorylated by the enzyme from E. brunetti. In contrast to the inhibitor specificity, the substrate activities of these nucleosides do not correlate well with their in vivo anticoccidial activity. Structure-activity relations are discussed.

L7 ANSWER 112 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1980:33780 CAPLUS Full-text
DOCUMENT NUMBER: 92:33780
TITLE: Design of species- or isozyme-specific enzyme inhibitors. 2. Differences between a bacterial and a mammalian thymidine kinase in the effect of thymidine substituents on affinity for the thymidine site
AUTHOR(S): Hampton, Alexander; Kappler, Francis; Chawla, Ram R.
CORPORATE SOURCE: Fox Chase Cancer Cent., Inst. Cancer Res., Philadelphia, PA, 19111, USA
SOURCE: Journal of Medicinal Chemistry (1979), 22(12), 1524-8
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal
LANGUAGE: English

AB A few new and a number of previously synthesized monosubstituted thymidines and uridines were evaluated as inhibitors of Escherichia coli and hamster thymidine kinase [72163-57-6]. Affinity for the enzymic thymidine binding sites was assessed from apparent enzyme- inhibitor dissociate consts. (Ki values, for inhibitions competitive with respect to thymidine at near-saturating ATP levels) or I50 values (for noncompetitive inhibitions). 5'-C-(Acetamidomethyl)- and 5'-C-(propionamidomethyl)thymidine epimers inhibited both enzymes competitively, and the extra Me present in the propionamido derivs. resulted in 7.5- and 9-fold differential effects on binding. Thus, thymidine derivs. can bind to the thymidine sites of E. coli and hamster thymidine kinase in a species-selective manner. Structure-activity relations are discussed.

L7 ANSWER 113 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1979:604203 CAPLUS Full-text
DOCUMENT NUMBER: 91:204203
TITLE: Design of species- or isozyme-specific enzyme inhibitors. 3. Species and isozymic differences between mammalian and bacterial adenylate kinases in substituent tolerance in an enzyme-substrate complex
AUTHOR(S): Hampton, Alexander; Picker, Donald
CORPORATE SOURCE: Fox Chase Cancer Cent., Inst. Cancer Res., Philadelphia, PA, 19111, USA
SOURCE: Journal of Medicinal Chemistry (1979), 22(12), 1529-32
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
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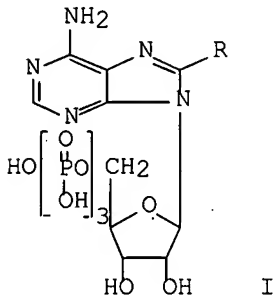
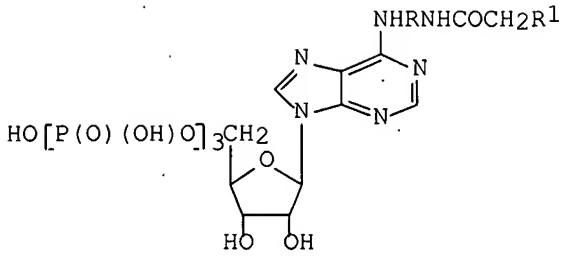


I

AB The ATP derivs. I (R = alkylthio, hydroxyalkylthio, or PhS) were prepared from tetra-Li 8-bromoadenosine 5'-triphosphate [71683-13-1] and the appropriate mercaptide and converted to the tetra Na salts. I and N6- ATP derivs. were evaluated as potential species- or isoenzyme-selective inhibitors of bacterial and mammalian adenylate kinase [9013-02-9]. The substituent attached at either N6 or C-8 influenced the affinity of the compds. for the enzymic ATP sites in both a species- and an isoenzyme-selective manner. Structure-activity relations are discussed.

L7 ANSWER 114 OF 114 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1976:554445 CAPLUS Full-text
DOCUMENT NUMBER: 85:154445
TITLE: Evidence for species-specific substrate-site-directed inactivation of rabbit adenylate kinase by N6-(6-iodoacetamido-n-hexyl)adenosine 5'-triphosphate
AUTHOR(S): Hampton, Alexander; Slotin, Lewis A.; Chawla, Ram R.
CORPORATE SOURCE: Inst. Cancer Res., Fox Chase Cancer Cent., Philadelphia, PA, USA
SOURCE: Journal of Medicinal Chemistry (1976), 19(11), 1279-83
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Seven adenosine 5'-triphosphate derivs. [I: R = (CH2)n, n = 5-8, or (CH2)2O(CH2)2; (CH2)2O(CH2)2O(CH2)2; R1 = H, I] were prepared from 6-chloropurine ribonucleoside 5'-phosphate by reaction with the appropriate diamine, followed by acylation by the resp. N-acylsuccinimide, conversion to the phosphorimidazolidate by reaction with 1,1'-carbonyldiimidazole in DMF, and reaction with tributylammonium pyrophosphate. Derivative II (I; n = 5, R1 = I) [60081-15-4] did not inhibit rabbit, pig, or carp adenylate kinase [9013-02-9]; derivative III (I; n = 6, R1 = I) [60081-16-5] at 0.79mM gave 76% inactivation of rabbit enzyme, while at 2.76mM pig and carp enzymes were unaffected; derivative IV (I; n = 7, R1 = I) [60322-29-4] at 1mM gave 14% inactivation of rabbit enzyme, but did not inactivate the other 2 enzymes; derivative V (I; n = 8, R1 = I) [60081-18-7] at 1mM inactivated all enzymes by 11-15%. No inactivation occurred with the acetamido derivative (I; n = 6, R1 = H) [60081-17-6] or with the other 2 derivs. There was no evidence of activation of III by rabbit enzyme or deactivation by pig or carp enzymes. Structure-activity relations were discussed.

=> log y